Proposed Re-evaluation Decision PRVD2010-02

Imazethapyr

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Table of Contents

Overview 1
Proposed Re-evaluation Decision for Imazethapyr 1
What Does Health Canada Consider When Making a Re-evaluation Decision? 2
What is Imazethapyr? 2
Health Considerations 3
Environmental Considerations 5
Value Considerations 6
Proposed Measures to Minimize Risk 6
Next Steps 7
Other Information 7
Science Evaluation 9
1.0 Introduction 9
2.0 The Technical Grade Active Ingredient, Its Properties and Uses 9
2.1 Identity of the Technical Grade Active Ingredient 9
2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient 10
2.3 Description of Registered Imazethapyr Uses 10
3.0 Impact on Human and Animal Health 11
3.1 Toxicological Summary 11
3.1.1 *Pest Control Products Act* Hazard Characterization 13
3.2 Occupational and Non-Occupational Risk Assessment 14
3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment 14
3.2.2 Occupational Exposure and Risk Assessment 14
3.2.3 Non-Occupational and Residential Exposure and Risk Assessment 16
3.3 Dietary Risk Assessment 16
3.3.1 Determination of Acute Reference Dose 17
3.3.2 Acute Dietary Exposure and Risk Assessment 17
3.3.3 Determination of Acceptable Daily Intake 17
3.3.4 Chronic Non-Cancer Dietary Exposure and Risk Assessment 18
3.3.5 Carcinogenic Dietary Exposure and Risk Assessment 18
3.4 Exposure from Drinking Water 18
3.4.1 Concentrations in Drinking Water 18
3.4.2 Drinking Water Exposure and Risk Assessment 18
3.5 Aggregate Risk Assessment 19
3.6 Incident Reports 19
4.0 Impact on the Environment 19
4.1 Fate and Behaviour in the Environment 19
4.2 Effects on Non-Target Species 20
4.2.1 Effects on Terrestrial Organisms 21
4.2.2 Effects on Aquatic Organisms 22

5.0 Value 22
5.1 Commercial Class Products 22
5.2 Domestic Class Products 22
5.3 Value of Imazethapyr 22
6.0 Pest Control Product Policy Considerations 23
6.1 Toxic Substances Management Policy Considerations 23
6.2 Formulants and Contaminants of Health or Environmental Concern 23
7.0 Summary 24
7.1 Human Health and Safety 24
7.1.1 Occupational Risk 24
7.1.2 Dietary Risk from Food 25
7.1.3 Dietary Risk from Drinking Water 25
7.1.4 Non-Occupational Risk 25
7.1.5 Aggregate Risk 25
7.2 Environmental Risk 25
7.3 Value 25
8.0 Proposed Regulatory Decision 25
8.1 Proposed Regulatory Actions 26
8.1.1 Proposed Regulatory Action Related to Human Health 26
8.1.2 Proposed Regulatory Action Related to Environment 28
8.1.3 Proposed Regulatory Action Related to Value 28
8.2 Additional Data Requirements 28
List of Abbreviations 29
Appendix I Registered Imazethapyr Products as of 25 August 2008 33
Appendix II Registered Uses of Imazethapyr as of 25 August 2008* 35
Appendix III Toxicology Assessment for Imazethapyr 37
Table 1 Toxicology Profile for Imazethapyr from PMRA and Foreign Reviews 37
Table 2 Summary of Risk Assessment Endpoints 42
Appendix IV Agricultural Mixer/Loader/Applicator and Postapplication Risk Assessment 43
Table 1 Inhalation Exposure Estimates and MOEs for Mixers/Loaders and Applicators of Products Containing Imazethapyr 43
Appendix V Dietary Exposure and Risk Estimates for Imazethapyr 45
Table 1 Aggregate Dietary (Food and Water) Exposure and Risk Estimates for Imazethapyr 45
Appendix VI Food Residue Chemistry Summary 47
Table 1 Radioactive Residue Level of Metabolites in Crops 48
Table 2 MRL and American Tolerances Summary 49
Table 3 Summary of Residue Analytical Methods in Plant Commodities 50
Table 4 Summary of Storage Stability Studies in Plants 53
Table 5 Summary of Crop Residues 54
Table 6 Summary of Maximal Animal Residues 56
Appendix VII Monitoring Data 59
Table 1 Summary of the Monitoring Studies Available for Imazethapyr 61

Appendix VIII Environmental Fate and Toxicity 65
Table 1 Fate and Behaviour of Imazethapyr in the Environment 65
Table 2 Toxicity of Imazethapyr to Non-Target Species 67
Table 3 Summary of Screening Level Risk Assessment of Imazethapyr to Terrestrial Invertebrates and Plants 71
Table 4 Refined Risk Assessment of Imazethapyr to Terrestrial Plants 71
Table 5 Screening Level Risk Assessment of Imazethapyr to Birds and Mammals 72
Table 6 Summary of Screening Level Risk Assessment of Imazethapyr to Aquatic Organisms 74
Table 7 Risk Quotient for Aquatic Vascular Plants Obtained From Spray Drift of Imazethapyr Used at Maximum Rate of Application 76
Table 8 Risk Quotient for the Aquatic Vascular Plant *Lemna gibba* Determined for Imazethapyr in Run-off from Water Modeling (PRZM-EXAM) 76
Table 9 Toxic Substances Management Policy Considerations—Comparison to Track 1 Criteria for Imazethapyr 78
Appendix IX Label Amendments for Products Containing Imazethapyr 79
References 81

Overview

Proposed Re-evaluation Decision for Imazethapyr

After a re-evaluation of the herbicide imazethapyr, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing imazethapyr for sale and use in Canada.

An evaluation of available scientific information found that, under the proposed conditions of use, products containing imazethapyr have value and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of imazethapyr, further risk-reduction measures are proposed for the labels of all products. No additional data are being requested at this time.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing imazethapyr registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for imazethapyr and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of imazethapyr.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[2] The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Health Canada's website at www.hc-sc.gc.ca/cps-spc/pest/index-eng.php.

Before making a re-evaluation decision on imazethapyr, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision document[5] on imazethapyr, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is Imazethapyr?

Imazethapyr is a selective systemic herbicide. It is registered for preplant, pre-emergence or postemergence use on terrestrial food and/or feed crops. Imazethapyr may be used alone or in co-formulation with imazamox or pendimethalin to control a broad spectrum of broadleaf and grassy weeds. It is applied once per year at a rate of 10 to 100 g a.e./ha by ground equipment only.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's *(a)* efficacy; *(b)* effect on host organisms in connection with which it is intended to be used; and *(c)* health, safety and environmental benefits and social and economic impact".

4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*

Health Considerations

Can Approved Uses of Imazethapyr Affect Human Health?

Imazethapyr is unlikely to affect your health when used according to the revised label directions.

Potential exposure to imazethapyr may occur through consuming food and water, working as a mixer/loader/applicator or by entering treated sites. The PMRA considers two key factors when assessing health risks: the dose levels where no health effects occur and the dose levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-fold higher (and often much higher) than levels to which humans are normally exposed when using imazethapyr products according to label directions.

Imazethapyr belongs to the imidazolinone family of herbicides which demonstrate a very low toxicity profile in mammals due to a plant-specific mode of action. While acute overexposures to imazethapyr resulted in low toxicity by the oral, dermal and inhalation routes, results showed that contact with the eye may cause mild eye irritation. To prevent overexposure, label directions must be followed.

Additional findings in repeat-dose animal studies, including those in pregnant animals, consisted of decreases in some blood parameters, body weight, body-weight gain and food consumption. Overall, there was no concern with respect to carcinogenicity, genotoxicity, neurotoxicity or reproductive toxicity.

When imazethapyr was given to pregnant animals, effects on the developing fetus were only observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to imazethapyr than the adult animal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake (ADI) is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to imazethapyr from residues in treated crops and drinking water, including the most sensitive subpopulation (children 1–2 years old) was estimated. Only long-term (chronic) exposure estimates were determined for different subpopulations representing different ages, genders and reproductive status. Acute and cancer dietary assessments were not required.

Aggregate chronic exposure (that is, imazethapyr from food and drinking water) represents 8.9% and 43.4% of the chronic reference dose for the general population and children 1–2 years old, respectively, when using drinking water modelling. As a result, chronic risks were below the PMRA's level of concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Based on metabolism data, the current residue definition in all commodities is the parent compound, imazethapyr (CL 263499 or BAS 685 H) (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid, expressed as ammonium salt.

For this residue definition, MRLs for imazethapyr are currently specified for kidney beans, lima beans, navy beans, pinto beans, runner beans, snap beans, soybeans, tepary beans, wax beans, which have a value of 0.1 ppm, and fenugreek and canola at a value of 0.05 ppm. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm.

Risks in Residential and Other Non-Occupational Environments

Residential and other non-occupational risks are not of concern.

Imazethapyr is not registered for use in any residential areas. Therefore, a non-occupational risk assessment was not required. Basic statements to reduce drift to residential areas were recommended.

Occupational Risks from Handling Imazethapyr

Occupational risks are not of concern when used according to the label directions.

Based on the precautions and directions for use on the current label and considering the use of appropriate protective equipment, the risk estimates associated with mixing, loading and applying activities meet current standards for all use scenarios and are not of concern. Additional personal protective equipment is not required beyond what is currently specified on the label.

Occupational postapplication risks are not of concern when used according to the revised label directions.

Occupational postapplication risk assessments consider exposures to workers entering treated agricultural sites. Based on the precautions and directions for use on the original product labels reviewed for this re-evaluation, postapplication risk to workers meets current standards and is not of concern. To meet current standards, a minimum 12-hour restricted-entry interval is proposed for all uses.

Environmental Considerations

What Happens When Imazethapyr Is Introduced Into the Environment?

Imazethapyr is mobile and persistent and poses a potential risk to terrestrial and aquatic vascular plants; therefore, additional risk reduction measures need to be observed.

When imazethapyr is applied for control of weeds in crops, some of it finds its way into soil and water. The chemical is persistent in soil, sediment and water and could carry over. Imazethapyr is mobile and has the potential to leach to groundwater. However, field evidence indicates that imazethapyr remains within the top 15 cm of the soil after application. Water monitoring of ponds and rivers have revealed residues from runoff, but at concentration below levels of concern for aquatic life. Two major transformation products are formed from the breakdown of imazethapyr in soil and aquatic systems, but their fate in the environment, especially of CL 290395 (Appendix VIII, Diagram 1), has not been fully characterized.

When imazethapyr is used for weed control in crops, there is a potential that sensitive plant species on land and in water may be exposed to the chemical as a result of the spray drift and runoff. Some of these species are sensitive to the chemical and would be adversely affected. In order to mitigate effects in non-target areas, spray buffer zones between the agricultural field and the non-target terrestrial or aquatic areas are required. The width of these buffer zones will be specified on the product label. Imazethapyr presents negligible risk to wild birds, mammals, bees, earthworms, fish, amphibians, aquatic invertebrates and algae because concentrations in the environments are expected to be at levels that are not harmful.

Value Considerations

What is the Value of Imazethapyr?

Imazethapyr continues to contribute to weed management in a variety of crops when used in accordance with the label directions.

Several major crops including canola, corn and lentils have been modified through mutagenesis followed by conventional breeding and selection to acquire imazethapyr tolerant traits (CLEARFIELD® traits). Imazethapyr has also been widely used in soybeans, field peas and processing peas. It is the only herbicide registered for the control of broadleaf weeds in chickling vetch and fenugreek. Moreover, imazethapyr is the only alternative for the control of grassy weeds in chickling vetch and fenugreek. Imazethapyr controls both grassy and broadleaf weeds in adzuki beans, lima beans, snap common beans and dry common beans while alternatives only control either grassy or broadleaf weeds. Although imazethapyr plays a role in mitigating resistance development in weeds to other herbicide groups, consideration has to be given to resistance management as more weed species are reported to be resistant to herbicides that inhibit acetolactate synthase (such as imazethapyr) than to herbicides having other modes of action.

Proposed Measures to Minimize Risk

The labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Further risk-reduction measures are being proposed to address potential risks identified in this assessment. These measures, in addition to those already identified on existing imazethapyr product labels, are designed to further protect human health and the environment.

Additional Key Risk-Reduction Measures

Human Health

- To protect workers entering treated fields, a 12-hour restricted-entry interval is being proposed for all formulations.
- Precautionary statements are being proposed to avoid drift to areas of human habitation or areas of human activity.

Environment

- Updated precautionary statements and terrestrial and minimal aquatic buffer zones (1 m) are being proposed for the protection of terrestrial and aquatic habitats that may contain sensitive plant species.

Next Steps

Before making a re-evaluation decision on imazethapyr, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

At the time that the re-evaluation decision is made, the PMRA will publish an Evaluation Report on imazethapyr in the context of this re-evaluation decision (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

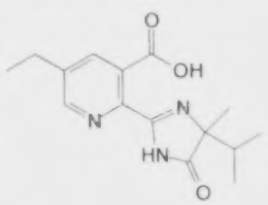
1.0 Introduction

Imazethapyr is a selective systemic herbicide. It belongs to the imidazolinone chemical family and is classified as a Group 2 herbicide. The herbicidal activity of imazethapyr is due to the inhibition of the plant enzyme acetolactate synthase, also called acetohydroxyacid synthase.

Following the re-evaluation announcement for imazethapyr, BASF Canada Inc., the registrant of the technical grade active ingredient and primary data provider in Canada, indicated that it intends to provide continued support for all uses included on the label of Commercial Class end-use products. There are no Domestic Class end-use products containing imazethapyr in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

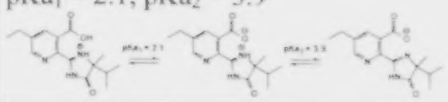
2.1 Identity of the Technical Grade Active Ingredient

Common name		Imazethapyr
Function		Herbicide
Chemical Family		Imidazolinone
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	(*RS*)-5-ethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid
2	**Chemical Abstracts Service (CAS)**	(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid
CAS Registry Number		81335-77-5
Molecular Formula		$C_{15}H_{19}N_3O_3$
Structural Formula		
Molecular Weight		289.33 amu

Identity of relevant impurities of human health or environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including Toxic Substances Management Policy (TSMP) Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 60°C	$<1 \times 10^{-7}$ mm Hg at 60 °C
Ultraviolet (UV)/visible spectrum	pH λ_{max} (nm) ε (Abs M^{-1} cm^{-1}) 2 240 10400 7 268 7200 There is absorption between 290–750 nm
Solubility in water at 25°C	1.4 g/L
n-Octanol–water partition coefficient at 25°C	pH log K_{ow} 5 1.04 7 1.49 9 1.20
Dissociation constant	$pKa_1 = 2.1$, $pKa_2 = 3.9$ 

2.3 Description of Registered Imazethapyr Uses

Appendix I lists all imazethapyr products that are registered under the authority of the *Pest Control Products Act*, specifically including one technical grade active ingredient and 10 Commercial Class end-use products. Eight of the Commercial Class end-use products contain imazethapyr alone and the remaining two are co-formulated either with imazamox or pendimethalin.

Appendix II lists all the uses for which imazethapyr is presently registered. All uses were supported by the registrant at the time of initiation of re-evaluation and were, therefore, considered in the health and environmental risk assessments. Also presented is whether any of the uses were added through the PMRA Minor Use Program. While currently supported by the registrant, the data supporting these minor uses was originally generated by a user group.

Uses of imazethapyr belong to the following use site categories: terrestrial food crops and terrestrial feed crops. The crops specifically include field peas, soybeans (including glyphosate tolerant varieties with Roundup Ready® gene), dry common beans (kidney, cranberry, Dutch brown, black, yellow eye, white, pinto, pink, and red beans), adzuki beans, lima beans, imazethapyr and imazamox-tolerant canola (for example canola varieties with the CLEARFIELD® trait), imazethapyr tolerant corn (that is CLEARFIELD® BRANDS), imazethapyr and imazamox tolerant lentils (that is lentil varieties with CLEARFIELD® trait), fenugreek (for seed use only), processing peas (succulent peas), snow peas, snap common beans, chickling vetch/grass pea, alfalfa grown for seed (seedling and/or established), and newly seeded purestand alfalfa for forage or seed production.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. The health effects noted here were observed in animals at dose levels at least 100-fold (often much higher) above levels to which humans are normally exposed through use of products containing this chemical.

3.1 Toxicological Summary

The toxicology database for imazethapyr is primarily based on previous reviews completed by the PMRA and the United States Environmental Protection Agency (USEPA), and in the United Kingdom on studies submitted by the registrant. Available studies were conducted between 1985 and 1989 in accordance with the accepted international testing protocols and Good Laboratory Practices at that time. The scientific quality of the data is adequate and the database is considered sufficient to define the toxic effects that may result from exposure to this chemical. The purity of imazethapyr used in the toxicity studies was 91.2%; the exceptions were the metabolism studies with a purity range of 98.6–99.8%. The different purities of imazethapyr were not expected to have an impact on the relevance of the results to hazard characterization.

Imazethapyr belongs to the imidazolinone family of herbicides, which demonstrate a very low toxicity profile in mammals due to a plant-specific mode of action. Imazethapyr disrupts protein synthesis via the inhibition of acetohydroxyacid synthase, an enzyme not found in mammalian tissues. Subsequently, the interference with DNA synthesis and cell growth that occurs in plants exposed to imazethapyr does not occur in mammalian species.

When orally administered, imazethapyr is rapidly absorbed and excreted, demonstrated by the rapid urinary clearance of the compound. The bulk of excretion occurs via the urine with the parent compound excreted virtually unchanged. Approximately 3% of the excreted product was the primary metabolite CL 288511, a 1-hydroxyethyl derivative of the parent compound (AC 263499). This metabolite was the only identified product excreted other than the parent compound. The only toxicology study involving the metabolite was an oral acute toxicity study, where it was found to be less acutely toxic than the parent compound. Imazethapyr did not have

any appreciable accumulation in tissues of the test animals, consistent with the rapid absorption/ urinary excretion and lack of metabolic breakdown of this compound in the metabolism studies.

Imazethapyr shows low acute oral toxicity in all species tested. Low acute toxicity was also demonstrated with the dermal and inhalation routes of exposure. It was a mild eye irritant in rabbits but was not irritating or sensitizing to skin in rabbits and guinea pigs respectively. There were no remarkable clinical signs noted with respect to the acute toxicity studies mentioned in the database.

Repeat-dose studies conducted in various species (mouse, rat and dog) and durations (subchronic and chronic) produced low-grade toxicity, with no indication of sensitivity for any particular species. Effects on body weight and body-weight gain were observed across all species and were in most cases the critical effects used to establish the NOAEL for the study in question. Other treatment related observations included reduced blood parameters (red blood cell, haemoglobin and packed cell volume counts) in females of the one-year dog study. Spleen discolouration, which was correlated microscopically with areas of capsular thickening (characterized by fibrosis), pigmented macrophages and inflammatory cells were found in high dose females of the same study.

There was also an increased incidence of uterine endometrial cysts at the high dose in a 13-week dietary rat study. Given the uterine effects seen in the 2-generation reproduction study (increase in haemosiderin deposits; single incidence of endometrial stromal polyp of the uterus/cervix), the data suggested a pattern or targeted effect. Due to the fact that there were no treatment related increases of uterine findings in the chronic study, the finding of the cysts in the 13-week study are not unequivocally linked to treatment. However, concern does remain due to the high incidence relative to the concurrent controls and the lack of historical controls providing evidence to the contrary.

Short-term dermal toxicity data in the rabbit revealed an absence of treatment-related effects at the highest dose tested. No repeat dose studies were available for the inhalation route of exposure.

The developmental toxicity studies in rats and rabbits showed no evidence of teratogenicity and no additional sensitivity of the fetus following in utero exposure to imazethapyr. There were some developmental effects noted, namely increases in pelvic cavitation or increases in the observations of intranasals (extra ossification sites present between nasals) in the rat and rabbit studies, respectively. Decreases in offspring body weights both on a litter and individual basis, occurred at the same dose level as the ossification effects. Maternal findings included decreases in body weight, body-weight gain and food consumption in both the rabbit and rat studies. However, the rabbit developmental study results, included maternal deaths and abortions at the high dose, which was the limit dose (1000 mg/kg bw/day) for this study type.

Parental effects in the 2-generation reproduction study included an increase in haemosiderin deposits and a single incidence of endometrial stromal polyp of the uterus/cervix at the high dose, both considered non-adverse. The findings for the offspring (both F1 and F2) included decreases in body weight on postnatal day 21 at levels showing no parental toxicity. As the

offspring begin to consume treated diet by this time point, the body weight results likely reflect the higher exposure per unit body weight that the pups receive relative to the adults, rather than an age-related sensitivity. Additionally, as milk intake and dietary consumption are occurring concurrently, there are now two likely sources of compound intake which could contribute to the body weight effects observed in the offspring.

There was no evidence of oncogenicity or genotoxicity in the mammalian toxicology database. Although a recent epidemiology study reported an association for increased risk (2-3-fold) of colon and bladder cancer among applicators of imazethapyr, these findings are inconsistent with the low grade toxicity observed in the broad range of mammalian toxicity studies, including studies that specifically examine carcinogenic potential. The study authors also noted that there was no biologic or experimental evidence to indicate that imazethapyr was carcinogenic, thus necessitating further examination in both the toxicology and epidemiology fields. In the absence of any causal relationship, imazethapyr is not considered carcinogenic.

Results of the toxicity tests conducted with imazethapyr, along with the toxicity endpoints used in risk assessment are summarized in Appendix III, Table 1 and Table 2.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, extensive data were available on imazethapyr including prenatal developmental toxicity studies in rats and rabbits, and a multi-generation reproduction study. There were no triggers to warrant a study to investigate developmental neurotoxicity.

With respect to potential pre-and postnatal toxicity, there was some indication of increased susceptibility in the offspring compared to parental animals in the reproduction study, based on slight decreases in F1 and F2 generation pup body weights. However, as the decreased body weight in the pups relative to the parents occurred at postnatal day 21, the pups experienced an increased compound intake at this time likely as a reflection of the higher exposure per unit body weight that the pups receive relative to the adults as well as the simultaneous exposure to imazethapyr via maternal milk and dietary consumption. The result is a probable enhancement of toxicity based on higher than intended compound intake, rather than an age related sensitivity. No teratogenicity or sensitivity of the fetus was observed in the rat or rabbit developmental toxicity study. The abortions in the dams of the rabbit developmental study that occurred late in gestation were associated with indications of maternal toxicity and occurred in animals tested at the limit dose (1000 mg/kg bw/day). In the rat, developmental delays (reduced fetal weights and ossification) were observed at dose levels that elicited clinical signs of toxicity in the maternal animals. Consequently, there was a low level of concern for pre- or postnatal toxicity associated

with imazethapyr. Given the low level of concern for pre- and postnatal toxicity and the completeness of the database, the *Pest Control Products Act* factor is reduced from 10-fold to 1-fold.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

3.2.1.1 Short- and Intermediate-term Dermal Risk Assessment

No dermal endpoint has been identified on the basis of a lack of toxicity in the dermal study and a lack of other toxicological endpoints of concern.

3.2.1.2 Short- and Intermediate-term Inhalation Risk Assessment

The 13-week dietary dog study is being used as a surrogate study due to the lack of a repeat-dose study for the inhalation route. The critical effects from this particular study include biologically significant reductions in body weight, body-weight gain and food consumption at 300 mg/kg bw/day; the NOAEL was 125 mg/kg bw/day. No long-term inhalation endpoint is required on the basis of the current use pattern.

A target MOE of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation, and 10-fold for intra-species variability. This value was considered to be protective of all worker populations including women who may be pregnant or breast feeding.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to imazethapyr through mixing, loading or applying the herbicide during normal use, and when entering a treated site to conduct activities such as scouting and/or handling treated crops. A quantitative dermal risk assessment was not required as no dermal toxicity endpoint was identified on the basis of a lack of systemic toxicity in the dermal study and lack of other toxicological endpoints of concern.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders and applicators. The following supported uses were assessed:

- Mixing and loading solutions and emulsifiable concentrate formulations for application to field crops
- Mixing and loading soluble granule and wettable granule formulations for application to field crops
- Mixing and loading the soluble granule and wettable granule formulations in water soluble packaging for application to field crops
- Applying the liquids as sprays to field crops by groundboom sprayer

Occupational handlers of imazethapyr include farmers and custom agricultural applicators who mix, load and apply the herbicide. As only one application is permitted per year, the duration of exposure for farmers is expected to be short-term (up to 30 days). In the case of custom applicators, the duration of exposure may be intermediate (from one to six months). As no quantitative dermal risk assessment was required, only inhalation exposure of occupational handlers was assessed.

The following level of personal protective equipment (PPE) is currently specified on all labels for mixers, loaders and applicators:

Baseline PPE: Long pants, long sleeved shirt during all activities and chemical-resistant gloves for mixing and loading, clean-up and repair.

The PMRA estimated handler inhalation exposure based on the best available data at this time. The assessment might be refined with product-specific exposure data, or biological monitoring data.

No chemical specific exposure studies were available for use in the re-evaluation of imazethapyr. Thus, appropriate inhalation exposures were estimated using the *Pesticide Handlers Exposure Database (PHED), Version 1.1*. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE.

In some cases, PHED did not contain exact datasets to estimate exposure to workers. In those cases, surrogate data were used. Exposure for mixing and loading soluble granules and wettable granules was estimated using the dry flowable data. Exposure for mixing and loading soluble granules in water soluble packaging and wettable granules in water soluble packaging was estimated using wettable powder in water soluble packaging data.

PHED unit exposures coupled with information on the amount of imazethapyr handled per day was used to estimate handler exposure. The amount handled per day is based upon the maximum label application rate and default assumptions on the area (of crop) which can reasonably be treated in one day.

Calculated MOEs (summarized in Appendix IV) exceed the target MOE for all exposure scenarios and are not of concern. It is indicated on the current label that a long-sleeved shirt, long pants and chemical-resistant gloves must be worn when handling the product. No further mitigation measures are required. Regulatory actions are described in Section 8.0.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considers exposure to workers entering treated agricultural sites. A quantitative postapplication risk assessment was not conducted as no dermal toxicity endpoint was identified on the basis of lack of systemic toxicity in the dermal study and lack of other toxicological endpoints of concern. Inhalation exposure is expected to be negligible due to the low vapour pressure of imazethapyr.

3.2.3 Non-Occupational and Residential Exposure and Risk Assessment

3.2.3.1 Non-Occupational Handler and Risk

There are no domestic class products; therefore, a non-occupational handler assessment was not required.

3.2.3.2 Bystander Exposure and Risk

For bystanders, exposure is expected to be much less than that of field workers and is considered negligible.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to imazethapyr from potentially treated imports is also included in the assessment.

These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting the use of a pesticide when its risk exceeds 100% of the reference dose. Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

Residue estimates used in the dietary risk assessment may be conservatively based on the maximum residue limits (MRL). They may also be based on the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program.

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.03), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix V and Appendix VI.

3.3.1 Determination of Acute Reference Dose

No acute reference dose was required based on imazethapyr's low acute toxicity.

3.3.2 Acute Dietary Exposure and Risk Assessment

No acute dietary exposure and risk assessment was conducted as no acute reference dose was determined.

3.3.3 Determination of Acceptable Daily Intake

To estimate dietary risk from repeat exposure, the 2-year chronic/oncogenicity study in rats was selected. The critical effect is a biologically significant decrease in body weight and body-weight gain in the female rats at 276 mg/kg bw/day; the NOAEL was 56 mg/kg bw/day. A total uncertainty factor of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available. An assessment of the data suggested a low level of concern for pre- and postnatal toxicity. The *Pest Control Products Act* factor was reduced from 10-fold to 1-fold based on the rationale provided in the *Pest Control Products Act* Hazard Consideration section above, yielding a composite assessment factor of 100. The ADI was calculated to be 0.56 mg/kg bw/day (56 mg/kg bw/day ÷ 100) and is considered to be protective of all populations including infants and children. There is a 700 fold margin between the ADI and the NOAEL for body weight effects in the offspring of the 2-generation rat reproduction study.

3.3.4 Chronic Non-Cancer Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary exposure is acceptable.

Deterministic chronic dietary exposure analyses were performed to determine the exposure and risk estimates resulting from the registered agricultural commodities. Maximum residue limits as well as empirical processing factors (DEEM defaults) were used.

Based on unrefined, theoretical and conservative residue data, the chronic potential daily intake from food only, accounted for less than 43.1% of the ADI for all subpopulations, whereas the aggregate (food and water) exposure did not exceed 43.4% of the ADI for all subpopulations, and are not of concern.

3.3.5 Carcinogenic Dietary Exposure and Risk Assessment

A cancer risk assessment was not conducted because the imazethapyr database did not suggest any carcinogenic potential in mice or rats.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of imazethapyr in potential drinking water sources (groundwater and surface water) were estimated using computer simulation models. For residues in groundwater, chronic exposure concentrations predicted by pesticide root zone model/exposure analysing modeling system (PRZM/EXAMS) were estimated to be 41 µg a.e./L. For residues in reservoirs and in dugouts, chronic exposure concentrations predicted were estimated to be 1.2 µg a.e./L and 12.1 µg a.e./L, respectively.

3.4.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure was considered in the chronic dietary assessment as both food and water consumption data and residue estimates were included in the assessments. In the chronic assessment, residues in drinking water were based on the highest yearly EEC (41 µg a.e./L). The drinking water estimates were incorporated directly in the aggregate dietary exposure assessment.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation). As there are no residential or other non-occupational uses of imazethapyr, aggregate exposure is from dietary and drinking water exposures only.

Deterministic aggregate chronic (food and water) exposure accounted for less than 43.4% of the ADI for all subpopulations. Therefore, it is not of concern.

3.6 Incident Reports

Starting 26 April 2007 registrants are required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death. The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product. Incident reports reflect the observations and opinion of the person reporting it and the Incident Reporting Program does not include validation of the reports. The PMRA collects incident reports in an effort to establish trends and the publishing of individual reports should not be considered as a statement of causality.

As of 1 December 2008, the PMRA incident report database contained seven reported minor incidents with a potential exposure due to packaging failure that leaked during transport or storage. There are no reports of any exposure incident associated with the leaks and none had an adverse effect reported on human health.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties (Section 2.2), imazethapyr is very soluble in water, has a very low potential for volatilization from moist soils or water surfaces under field conditions, and is not likely to bioaccumulate in organisms. Environmental fate data for imazethapyr are summarized in Appendix VIII, Table 1. Imazethapyr is relatively stable to hydrolysis at all environmentally relevant pHs. Phototransformation is not a major route of transformation in soil but could be a major route of transformation in water where a major transformation product 5-Ethyl 3-pyridine carboxylic acid (CL 290084) is formed during the process (Appendix VIII, Diagram 1).

Imazethapyr is not susceptible to biotransformation and is persistent in soil and water under aerobic and anaerobic conditions. The compound could carry over. Laboratory studies on adsorption/desorption and Thin Layer Chromatography studies indicate that the compound has the potential to be highly mobile. In terrestrial field studies conducted in Canada, varying degrees of detection in the soil horizon have been identified. The extent of leaching for imazethapyr is influenced by soil pH, organic matter and clay content altogether. The potential for leaching is prominent in low organic and coarse textured soils. However, several field dissipation studies showed no detection of imazethapyr beyond 15 cm depth.

Canadian water monitoring data show detection of imazethapyr in surface water and groundwater with concentrations ranging from 0.0009 to 0.84 µg/L and 0.114 µg/L, respectively (Table 1. Appendix VII).

4.2 Effects on Non-Target Species

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are calculated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is protection at the community, population or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial Organisms

Assessment of the risk of imazethapyr to terrestrial organisms was based upon an evaluation of toxicity data of the compound to earthworms (acute contact), bees (acute contact), two species of birds (acute oral, dietary and chronic), two species of mammals (acute oral, sub chronic and chronic) and 10 species of terrestrial plants (seedling emergence and vegetative vigour). A summary of terrestrial toxicity data for imazethapyr is presented in Appendix VIII, Table 2. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with imazethapyr.

For birds and mammals, the most sensitive endpoints (acute oral, dietary and reproduction) were used to extrapolate toxicity endpoints for birds and mammals of different sizes (20, 100 and 1000 g for birds and 15, 35 and 1000 g for mammals). To address differences in species sensitivity, the acute oral LD_{50} and dietary LC_{50}, converted to daily dose, were further divided by a safety factor of 10. The screening level assessment used relevant food categories representing specific feeding guilds for each bird and mammal size class consisting of 100% of a particular dietary item (plants, grain/seeds, insects and fruit). Estimated daily exposures (EDE) for each bird and mammal size were calculated based on EECs for each feeding preference group at each application rate and food ingestion rate. The screening level risk assessment indicated that exposure to imazethapyr does not pose a risk to terrestrial invertebrates, mammals and birds. Appendix VIII, Table 3 and Table 5 summarize the risk assessment from imazethapyr to terrestrial organisms. However, as imazethapyr is a herbicide, adverse effects to non-target terrestrial plants are expected. Seedling emergence and vegetative vigour studies indicated that some species did not follow normal growth patterns and consequently detrimental effects (failure to recover) were observed at low rates of application. The effects were likely due to the ability of imazethapyr to inhibit the plant enzyme acetolactate synthase, hence stopping cell division and plant growth by blocking branched chain amino acid biosynthesis. No toxicity studies conducted with transformation products were available for review.

Imazethapyr herbicide poses a risk to non-target terrestrial plants. The LOC was exceeded by 27.3 times at the lowest application rate (30 g a.e./ha) for the onion (*Allium cepa*). As a result, a refinement of the risk assessment was conducted taking into consideration the concentrations of imazethapyr that could be present in terrestrial habitat directly adjacent to the application field through spray drift. Spray drift data for a medium ASAE droplet size, as is generally used in ground boom applications of herbicides, indicate that the maximum amount of spray that will drift one metre down wind from the point of application during spraying is 6%. The offsite EECs for imazethapyr were calculated by using this percent drift, the highest rate of application (100 g a.e./ha) and a species sensitivity distribution approach (SSD with HC_5 = 4.04 g a.e./ha). Based on this refinement to the assessment, imazethapyr was found to pose a risk to non-target terrestrial plants directly adjacent to the application field. Exceedance of the LOC was reduced to 1.5 times from 27.3 times at the highest application rate for onion. Buffer zones will be required to mitigate the risk of imazethapyr to non-target terrestrial plants. Appendix VIII, Table 4 summarizes the refined risk assessment of imazethapyr to non-target terrestrial plants.

4.2.2 Effects on Aquatic Organisms

Acute and chronic risk was based on an evaluation of toxicity data on imazethapyr for nine freshwater species (one invertebrate, four fish, three algae and one vascular plant) and four marine species (one mysid, one oyster, one fish and one alga). No toxicity data on the transformation products were available for aquatic studies. For the risk assessment, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with imazethapyr. The endpoints were derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of 10 for fish.

The screening level risk assessment presented in Appendix VIII, Table 6 indicated that imazethapyr poses a negligible risk to freshwater and marine invertebrates and fish based on acute and chronic toxicity, to amphibians (fish surrogate data) and to algae. However, as imazethapyr is a herbicide, adverse effects to non-target aquatic plants are expected. The risk assessment was conducted using data for the most sensitive freshwater and marine species.

A screening level assessment showed that there was a potential risk to the vascular plant duckweed at the highest rate. The LOC was exceeded by 2.5 times at the application rate of 100 g a.e./ha for the duckweed. A refined risk assessment was based on exposure from spray drift (6% of applied amount) and runoff, which reduced the exceedance of the LOC to 0.15 times. Risk quotients for immersed aquatic vascular plant determined for imazethapyr from both, spray drift and runoff showed RQ values <1 (AppendixVIII, Table 7 and Table 8) indicating that the LOC was not exceeded for duckweed. Water Modeling data (PRZM-EXAMS) were used in the environmental risk assessment to estimate the $EEC^{90th\ percentile}$ (of the 21-day average) for the different regions of Canada where imazethapyr is expected to be used (see Appendix VII for more explanation).

5.0 Value

5.1 Commercial Class Products

All imazethapyr uses are supported by the registrant. There are no risk concerns for any of the registered uses. Consequently, no analysis was needed to identify alternatives to the use of imazethapyr.

5.2 Domestic Class Products

There are no Domestic Class products containing imazethapyr.

5.3 Value of Imazethapyr

Several major crops including canola, corn and lentils have been modified through mutagenesis followed by conventional breeding and selection to acquire imazethapyr tolerant traits (CLEARFIELD® traits). Imazethapyr has also been widely used in soybeans, field peas and processing peas. It is the only herbicide registered for the control of broadleaf weeds in chickling

vetch and fenugreek. Moreover, imazethapyr is the only alternative for the control of grassy weeds in chickling vetch and fenugreek. Imazethapyr controls both grassy and broadleaf weeds in adzuki beans, lima beans, snap common beans and dry common beans while alternatives only control either grassy or broadleaf weeds. Although imazethapyr plays a role in mitigating resistance development in weeds to other herbicide groups, consideration has to be given to resistance management as more weed species are reported to be resistant to herbicides that inhibit acetolactate synthase (such as imazethapyr) than to herbicides having other modes of action.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The TSMP is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy—persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the review process, imazethapyr and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Imazethapyr does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix VIII, Table 9 for comparison with Track 1 criteria.

- Imazethapyr is not expected to form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[7] The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies

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[6] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

[7] *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions* and *Part 3 Contaminants of Health or Environmental Concern.*

[8] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

and regulations including: DIR99-03 and DIR2006-02[9], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade imazethapyr does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

- The end-use products Pursuit, Pursuit 240, Pursuit 70DG, Conquest B, Guardsman Gladiator and Odyssey do not contain any formulants of health or environmental concern identified in the *Canada Gazette*. However, the end-use products Valor, Valor-1 do contain an aromatic petroleum distillate. Therefore, the label for the end-use products Valor and Valor-1 will include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for imazethapyr is adequate to define the toxic effects that may result from exposure to imazethapyr. There was no evidence that imazethapyr was carcinogenic, neurotoxic, genotoxic or teratogenic. The main effects observed in the database were decreases in body weight, body-weight gain and food consumption. There were effects observed on blood parameters as well; however, these observations were not widespread like those on body weight and food consumption. When imazethapyr was given to pregnant animals, no sensitivity of the fetus was observed. Exposed offspring were observed having decreases in body weight on postnatal day 21 at levels showing no parental toxicity. However the body weight results likely reflect the higher exposure that the pups receive relative to the adults, rather than an age-related sensitivity. The risk assessment protects against these effects by ensuring that the level of exposure is well below the lowest dose at which these effects occurred in animal tests.

7.1.1 Occupational Risk

The occupational application and postapplication risks are acceptable for the exposure scenarios involving the use of imazethapyr. The calculated margins of exposure for application are all above the PMRA target assuming that workers wear baseline personal protective equipment, as is currently specified on the labels. A postapplication risk assessment was not required, as risks are expected to be negligible.

[9] DIR2006-02, PMRA Formulants Policy.

7.1.2 Dietary Risk from Food

The chronic food risk assessment demonstrates that there were no dietary concerns for any population subgroup in Canada, including infants, children, teenagers, adults and seniors. In addition, no dietary concerns were evident for nursing or pregnant females or based on gender in general.

7.1.3 Dietary Risk from Drinking Water

The potential for the contamination of drinking water with imazethapyr is expected to be minimal. Chronic risk estimates associated with exposure of imazethapyr from water are not of concern.

7.1.4 Non-Occupational Risk

Imazethapyr is not registered for use in any residential areas; therefore, a non-occupational risk assessment was not required.

7.1.5 Aggregate Risk

The aggregate risk from food and drinking water is not of concern.

7.2 Environmental Risk

Imazethapyr is persistent in most soils and aquatic systems and could carry over. It is also mobile and has the potential to leach to groundwater. A screening level risk assessment indicates that it is not a risk to terrestrial and aquatic organisms, except for plants. A refined risk assessment for non-target terrestrial and aquatic plants indicates that spray drift will have adverse effects on non-target terrestrial plants. The risk quotients in the refined assessments of non-target terrestrial plant exceeded the LOC by a factor of 1.5 (RQs >1) but remained under level of concern (RQ <1) for the aquatic plants.

7.3 Value

From the value perspective, imazethapyr is acceptable for continued registration.

8.0 Proposed Regulatory Decision

After a re-evaluation of the herbicide imazethapyr, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing continued registration of imazathepyr products for sale and use in Canada provided that the mitigation measures for health and environment described in this document are implemented.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that the dietary and drinking water risks and worker risks during mixing, loading and application are acceptable for all uses provided that the mitigation measures listed in this section are implemented.

8.1.1.1 Residue Definition for Risk Assessment and Enforcement

The *Pest Control Products Act* currently lists the residues definition of imazethapyr for enforcement as the parent compound (CL 263499 or BAS 685 H) (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid, expressed as ammonium salt.

As the metabolites CL 288511 and CL 182704 are expected to be present in higher concentrations than the parent imazethapyr, for the determination of the risk assessment, a residue definition expressed as the sum of the residues of the herbicide imazethapyr, 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo- 1H-imidazol-2-yl]-5-ethyl-3-pyridine carboxylic acid; its metabolite CL 288511, 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-(1-hydroxyethyl)-3-pyridine carboxylic acid; and its metabolite CL 182704, 5-[1-(beta-D-glucopyranosyloxy)ethyl]-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-3-pyridinecarboxylic acid, applied as its acid or ammonium salt, will be used. Any future magnitude of residue data must include residue determinations of the established residue definition for risk assessment.

8.1.1.2 Maximum Residue Limits for Imazethapyr in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian MRLs and to remove those that are no longer supported.

The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as those required to support Canadian food use registrations. In addition, the PMRA requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed and to ensure they would not result in unacceptable health risks.

The Canadian MRLs for imazethapyr are established for kidney beans, lima beans, navy beans, pinto beans, runner beans, snap beans, soybeans, tepary beans, wax beans and peas, all of which have a value of 0.1 ppm. MRLs were proposed and established in 2008 for canola and fenugreek at a level of 0.05 ppm (EMRL 2008-25 and EMRL 2008-27).

Imazethapyr is registered for use in Canada on the following crops: processing peas; soybeans; snow peas; edible beans – kidney beans, cranberry beans, Dutch brown beans, black beans, yellow eye beans, white beans, adzuki beans and lima beans (Ontario only); imazethapyr tolerant canola (CLEARFIELD® brands); imazethapyr tolerant corn (CLEARFIELD® brands); alfalfa forage; seedling and established alfalfa for seed; snap beans; field peas; dry beans – Pinto, pink and red; chickling vetch/grass pea; imazethapyr and imazamox-tolerant canola (Prairie Provinces and Peace River, British Columbia); imazethapyr and imazamox-tolerant lentils (CLEARFIELD® trait); field peas (Prairie Provinces and Peace River, British Columbia) and fenugreek (Prairie Provinces and Peace River, British Columbia).

Where no specific MRL is established for a pest control product under the *Pest Control Products Act*, subsection B.15.002(1) of the Food and Drug Regulations applies. This requires that residues do not exceed 0.1 ppm, which is considered a general MRL for enforcement purposes. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*. If and when the general MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set for specific commodities.

Residue data were available to indicate that imazethapyr residue levels should not be detectable if imazethapyr is used according to good agricultural practice, as stipulated on the current product labels. The following MRLs for corn, lentils and legumes are currently being proposed based on the residues levels determined during field trials conducted in Canada and abroad and based on the sensitivity of the analytical method.

8.1.1.2 Table 1 Proposed MRLs for Plant Commodities

Commodity	Proposed MRL
Field corn	0.05 ppm
Dry lentil	0.05 ppm
Dry cranberry beans	0.1 ppm
Dry Dutch brown beans	0.1 ppm
Dry black beans	0.1 ppm
Dry yellow eyed beans	0.1 ppm
Dry white beans	0.1 ppm
Dry adzuki beans	0.1 ppm
Dry pink beans	0.1 ppm
Dry red beans	0.1 ppm

8.1.1.3 Proposed Mitigation for Mixer, Loader and Applicator Exposure and Postapplication Exposure

To meet current standards for protection of workers, a minimal restricted-entry interval is recommended. For all formulations, the following mitigation measures and label statements are proposed:

- Do not enter or allow entry into treated areas during the restricted-entry interval of 12 hours.

There may be potential for exposure to bystanders from drift following pesticide application to agricultural areas. In the interest of promoting best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift the following label statement is required:

- Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings.

8.1.2 Proposed Regulatory Action Related to Environment

The risk assessment has indicated adverse effects on non-target terrestrial plants. To reduce the effects of imazethapyr in the environment, mitigation in the form of precautionary label statements and spray buffer zones are proposed as listed in Appendix IX.

8.1.3 Proposed Regulatory Action Related to Value

Since resistance management recommendations are already stated on the end-use product labels, no further regulatory actions are proposed at this time with respect to the continued registration of imazethapyr.

8.2 Additional Data Requirements

No additional data are required at this point in time to support the continued registration of imazethapyr.

List of Abbreviations

↓	decrease
↑	increase
°C	degree(s) Celsius
♂	male
♀	female
λ	wavelength(s)
α	alpha
14-or ^{14}C	radioactive isotope 14 of the carbon atom
ABS	absorption
AD	administered dose
ADI	acceptable daily intake
a.e.	acid equivalent
amu	atomic mass units
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
2 ASU	240 g/L of aqueous solution with urea (formulation code by the company)
atm	atmospheres
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body-weight gain
CAF	composite assessment factor
CAS	Chemical Abstract Service
CE	capillary electrophoresis
CHO	Chinese hamster ovary cells
cm	centimetre(s)
d	day(s)
DACO	data code
DG	dispersible granule
DEEM-FCID	dietary exposure evaluation model – food consumption intake database
DNA	deoxiribonucleic acid
DRA	dietary risk assessment
DT_{50}	dissipation time to 50% (the dose required to observe a 50% decline in the test population)
EC	emulsifiable concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EbC_{50}	concentration that would inhibit biomass by 50% expressed as area under the growth curve
EDE	estimated daily exposure
EEC	expected environmental concentration
EMRL	established maximum residue limit
EXAMS	exposure analysis modeling system
F0	parental generation

F1	first filial generation
F2	second filial generation
g	gram(s)
GC	gas chromatography
GC-MSD	gas chromatography-mass selective detector
GC-NPD	gas chromatography-nitrogen phosphorous detector
h/hrs	hour(s)
ha	hectare
HC_5	hazardous concentration of 5%
Hg	mercury
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	high performance liquid chromatography
IMP	imazethapyr
IMZ	imazamox
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
K_d	adsorption coefficient
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	n-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population
LC/MS	liquid chromatography-mass spectroscopy detector
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LOC	level of concern
LOD	limit of detection
LOEC	lowest observed effect concentration
log K_{ow}	log octanol–water coefficient
LOQ	limit of quantitation
M	molar [6.02×10^{23} particle)
m	metre(s)
m^3	metre(s) cubed
mg	milligram(s)
mL	millilitre(s)
mm	millimetre(s)
mm Hg	millimetres of mercury
MOE	margin of exposure
MRID	document identifier for the USEPA
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NAWQA	United States Geological Survey National Water Quality assessment
nd	no detection
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration

NOEL	no observed effect level
NR	not required
OC	organic carbon content
OM	organic matter content
Pa	pascal
PAM	pesticide analytical manual
PCP#	registration number under the pest control products act
PEN	pendimethalin
pH	-log10 hydrogen ion concentration
PHED	pesticide handlers exposure database
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	part per million
PRVD	proposed re-evaluation decision
PRZM/EXAMS	pesticide root zone model/exposure analysing modeling system
RB	red blood cells
RQ	risk quotient
S9	mammalian metabolic activation system
s.d.	standard deviation
SG	soluble granule
SN	solution
SSD	species sensitivity distribution
TGAI	technical grade active ingredient
TRR	total radioactive residues
TSMP	toxic substances management policy
g	microgram(s)
USC	use site category
USEPA	United States Environmental Protection Agency
UV	ultraviolet/visible spectrum
WDG	water dispersible granule
WG	wettable powder formulation
WSP	water soluble packaging

Appendix I Registered Imazethapyr Products as of 25 August 2008

Registration Number	Marketing Class[1]	Registrant	Product Name	Formulation Type	Guarantee[2]		
					IMP	IMZ	PEN
21536	T	BASF Canada Inc.	Pursuit Technical Herbicide AC 263499	Dust or Powder	97%	-	-
21537	C		Pursuit Herbicide (Agricultural)	Solution	240 g/L	-	-
23844			Pursuit 240 Agricultural	Solution	240 g/L	-	-
24271			Pursuit 70DG Herbicide	Soluble Granules	70%	-	-
24407			Conquest B Herbicide (A component of Conquest Herbicide Tank Mix)	Soluble Granules	70%	-	-
25111			Odyssey WDG Herbicide	Wettable Granules	35%	35%	-
26287			Pursuit Herbicide for Soybeans (Agricultural)	Solution	240 g/L	-	-
27458			Valor-I Herbicide	Emulsifiable Concentrate	24.61g/L	-	300.22 g/L
28898			Pursuit 240 (Non-CLEARFIELD® crops)	Solution	240 g/L	-	-
28899			Pursuit 240 (CLEARFIELD® crops)	Solution	240 g/L	-	-
28923			Guardsman Gladiator	Solution	240 g/L	-	-

Discontinued products or products with a submission for discontinuation are not included.

1 T = Technical grade active ingredient; C = Commercial

2 IMP = imazethapyr; IMZ = imazamox; PEN = pendimethalin

Appendix II Registered Uses of Imazethapyr as of 25 August 2008*

Use Site Category	Site(s)		Weed(s)	Formulation Type[2]	Maximum Application Rate (g a.e./ha)	Use Supported?[3]
13 and 14 Terrestrial feed crops and terrestrial food crops	Field peas	Prairie Provinces and Peace River Region of British Columbia only	Broadleaf and grassy weeds as listed on the labels	SN	50	Y
				WG	15	
	Soybeans (including glyphosate tolerant that is varieties with Roundup Ready® gene)	Across Canada		SN	100	Y
				WG	15	
				SG	100	
				EC	88.1	
	Dry common beans (Kidney, cranberry, Dutch brown, Black, yellow eye, White, pinto, Pink and Red beans)	Across Canada		SN	75	Y and M
	Adzuki beans	Not in Prairie provinces		SN	75	M
	Lima beans	Ontario only		SN	75	M
	Fenugreek (for seed use only)	Prairie provinces and Peace River region of British Columbia only		WG	15	M
	Imazethapyr and imazamox tolerant canola (for example canola varieties with CLEARFIELD® trait)	Prairie Provinces and Peace River Region of British Columbia		SN	50	Y
				WG	15	
	Imazethapyr tolerant corn (that is CLEARFIELD® BRANDS)	Not in Prairie provinces		SN	75	Y
	Imazethapyr and imazamox tolerant lentils (that is , lentil varieties with CLEARFIELD® trait)	Prairie provinces and Peace River region of British Columbia only		WG	15	Y
14 Terrestrial food crops	Processing peas[1] (Succulent peas)	Not in Prairie provinces		SN	75	M
	Snow peas	Not in Prairie provinces		SN	75	M
	Snap common beans	Not in Prairie provinces		SN	75	M
	Chickling vetch/grass pea	Prairie provinces and Peace River region of British Columbia only		SN	50	M
13 Terrestrial feed crops	Alfalfa grown for seed (seedling and/or established)	Across Canada		SN	100	Y
				WG	15	
	Newly seeded purestand alfalfa for forage or seed production (establishment year in the black, grey wooded and irrigated brown soil zones)	Prairie provinces and Peace River region of British Columbia only		SN	50	Y

*Application is made once per year by ground equipment only. No aerial application is allowed for any uses.

1 According to the registrant, the processing peas on the label mean succulent peas or succulent shelled peas (*Pisum* spp.). They belong to Crop Subgroup 6B.

SN = Solution; WG = Wettable Granules; SG = Soluble Granules; EC = Emusifiable Concentrate.

Y = Use is currently registered and supported by the registrant.

M = Use was added as a User Requested Minor Use Label Expansion and is supported by the registrant.

Appendix III Toxicology Assessment for Imazethapyr

Table 1 Toxicology Profile for Imazethapyr from PMRA and Foreign Reviews

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption, distribution, metabolism and excretion Sprague-Dawley Rats 3 ♂/time point	Purity 99.8% ^{14}C-labelled Imazethapyr 5.7 mg/kg bw by gavage. Parameters assessed at 24, 48 and 72 hours		**Absorption:** Absorption of the chemical was very rapid in gastrointestinal tract, as inferred from the ~97% excretion of total radioactivity by 24 hrs **Metabolism:** No metabolites were found within 24 hrs using 2-dimensional thin layer chromatography, audioradiography and mass spectrometry **Distribution:** Peak concentration occurred at 24 hr timepoint with up to 0.02 ppm in blood and kidney. Other tested tissues and blood of the remaining animals did not elevate beyond 0.01ppm **Excretion:** 99.2% of the administered dose was found to be excreted by 72 hrs. 94.3% in urine and 4.9% in faeces, greatest amount of excretion came by 24 hrs, with 92% from urine and 4.5% from faeces. Based on these findings bioaccumulation would appear to not be a factor.
Absorption, distribution, metabolism and excretion Sprague-Dawley Rats 2/sex	Purity 99.2% ^{14}C-labelled imazethapyr 1000 mg/kg bw by gavage or 1000 mg/kg bw by gavage unlabelled imazethapyr for 3 days followed by labelled imazethapyr on 4th day (1/sex)		**Absorption:** Absorption of the chemical was very rapid in the g.i. tract as inferred from the excretion of total radioactivity by 24 hrs which was >97% **Metabolism:** 1.3–2.6% of recovered radioactivity was in the form of an a-hydroxyethyl derivative of imazethapyr (CL 288511), 97.0–98.5% or recovered radioactivity was in the form of the parent compound (AC 263499). **Excretion:** Almost 100% of the administered material was excreted (99.2–102.4% of dose). In urine 94.9% was excreted, while 5.8 was recovered in faeces by 96 hrs. Considered Supplementary
Absorption, distribution, metabolism and excretion Sprague Dawley CD Albino Rats 5/sex (treatment groups) 3/sex (controls)	Purity 98.6% ^{14}C-labelled imazethapyr 10 mg/kg bw via I.V. dose 10 mg/kg bw by gavage (single dose) 10 mg/kg bw by gavage (repeated dose) 1000 mg/kg bw by gavage (single dose)		**Absorption:** Rapid absorption as inferred from rapid urinary excretion, with the recovery of >90% of test material @ 24hrs and >95% @ 48hrs. **Distribution:** Treatment group animals did not register tissue concentrations greater than 1.0ppm in all tissues analysed. High dose females were the exception, with residues of 2.0ppm found in the carcass. Total residue levels for all dose groups and in all tissues accounted for less than 1.0% of the administered doses. Tissues analysed 7 days posttreatment. **Metabolism:** AC 263499 (parent compound) was the major urinary radioactive component recovered (ranging from 97% to 99%). The amount of metabolite CL 288511, the 1-hydroxyethyl derivative of AC 263499,

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
		represented 0.7–2.2% of the urinary radioactivity. The faecal radioactivity consisted of 16–49% AC 263499 and 21–42% CL 288511 indicating that a greater percentage of the AC 263499 was metabolized to form the hydroxyethyl metabolite in the gastrointestinal tract. Overall, 0.8–2.2% of the administered dose was converted into CL 288511 and excreted in the urine and faeces. **Elimination:** Greater than 94% of the dose was excreted within 48hrs, the overall recovery of total radiocarbon was 100.1% (s.d. 3.9%). After 7 days, urinary elimination ranged between 91–104% in both sexes and via all dose routes/regimens. Faecal elimination ranged from 1–4% in both sexes via gavage and intravenous administration and in low, high single and repeated doses.	
Acute Toxicity Studies			
Acute Oral Toxicity CF-1 Mice 10 ♀/group	Purity – 91.2%	**LD_{50}: >5000 mg/kg bw** "Depression" and diuresis in all animals 24hr postdosing	
Acute Oral Toxicity Rats 5/sex/group	Purity – 91.2%	**LD_{50}: >5000 mg/kg bw**	
Acute Oral Toxicity NZW Rabbits, 5 ♀	Purity – 91.2%	**LD_{50}: >5000 mg/kg bw**	
Acute oral Toxicity Charles River CD strain Rats 5/sex/group	**Metabolite CL 288511** Purity – 90–95% 5000 mg/kg bw	**LD_{50}: >5000 mg/kg bw**	
Acute Inhalation Toxicity Sprague-Dawley Rats 10/sex/group	Purity – 91.2% Trial conc. 4.83 mg/L air for 4 hrs via whole body exposure	**LC_{50} analytical: >3.27 mg/L** **LC_{50} gravimetric: >4.21 mg/L**	
Acute Dermal Toxicity NZW Rabbits 5/sex	Purity – 91.2%	**LD_{50}: >2000 mg/kg bw**	
Eye Irritation Rabbits 6 animals	Purity – 91.2%	Mild eye irritant	
Skin Irritation NZW albino Rabbits 6 animals	Purity – 91.2%	Non-irritating to intact skin	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Dermal Sensitization Hartley albino Guinea Pigs 12 ♂	Purity – 91.2% Buehler method	Not a sensitizer	
Subchronic Toxicity Studies			
21-day Dermal Toxicity NZW Rabbits 6/sex/group	Purity – 91% 0, 50, 200, 1000 mg/kg bw/day	**>1000**	No adverse effects due to treatment
13-week Dietary Toxicity Sprague-Dawley Rats 20/sex/group (plus an additional 10/sex/group for blood sampling)	Purity – 92.2% 0, 1000, 5000, 10000 ppm (0, 78/87, 393/ 427, 779/856 mg/kg bw/day ♂/♀)	**779 (♂)** **427 (♀)**	**856 mg/kg bw/day:** ↑ incidence of uterine endometrial cysts.
13-week Dietary Toxicity Beagle Dogs 4/sex/group	Purity – 92.1% 0, 1000, 5000, 10000 ppm (0, 25, 125, 300 mg/kg bw/day) mg/kg based on average ♂ & ♀ food intake	**125**	**300 mg/kg bw/day:** ↓body-weight gain; ↓food consumption (♂); ↓body weight (from week 9 onward to termination), ↓absolute and relative liver weight (♀). **No effect on haematology**
1-year Dietary Toxicity study Beagle Dogs 6/sex/group	Purity – 91.6% 0, 1000, 5000, 10000 ppm (0, 36/38, 177/198, 358/382 mg/kg bw/day ♂/♀)	**358 (♂)** **198 (♀)**	**≥198 mg/kg bw/day:** (♀) ↓ RBC, ↓ haemoglobin, ↓ packed cell volume (wk 26, 52) *-not considered adverse* **382 mg/kg bw/day:** (♀) ↓ RBC, ↓packed cell volume, ↓haemoglobin (all wk 6 to termination); Spleen discolouration, (♀) discolourations correlated microscopically with areas of capsular thickening characterized by fibrosis, pigmented macrophages and inflammatory cells; focal increase in hepato-portal fibrous tissue. (♀)

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Chronic Toxicity/Oncogenicity Studies			
78-week Oncogenicity Study, CD-1 Mice 65/sex/group	Purity – 91.2% 0, 1000, 5000, 10000 ppm (0, 164/205, 814/1027, 1676/2178 mg/kg bw/day ♂/♀)	**814 (♂)** **1027 (♀)**	**1676/2178 mg/kg bw/day:** ↓Body-weight gain; ↑mortality ♀; ↓lymphocytes ♀.
2-year Chronic Dietary Toxicity & Oncogenicity Sprague Dawley Rats 65/sex/group	Purity – 91.2% 0, 1000, 5000, 10000 ppm (0, 44/56, 222/276, 447/562 mg/kg bw/day ♂/♀)	**56 (♀)** **>447 (♂)**	**≥222/276 mg/kg bw/day:** ↓bw, ↓bwg in first 2 weeks of treatment ♂; ↓bw ↓bwg ♀
Reproductive and Developmental Toxicity Studies			
2-Generation (two-litter) Reproduction Sprague Dawley Rats 25/sex/group	Purity – 91.2% imazethapyr 0, 1000, 5000, 10000 ppm F_0 (0, 72/94, 352/485, 717/937 mg/kg bw/day ♂/♀) F_1 (0, 73/93, 372/500, 760/976 mg/kg bw/day ♂/♀)	**Parental** **717 (♂)** **485 (♀)** **Reproductive** **>937** **Offspring** **485**	**Parental** **F_0 937 & F_1 976:** Single incidence of endometrial stromal polyp of the uterus/cervix (F_0); ↑incidence of haemosiderin in the uterus/cervix (F_1). *-not considered adverse* **Reproductive effects:** No treatment related effects **Offspring effects:** **F_0 717/937 & F_1 760/976:** ↓ pup bw day 21 (F_1 & F2a)
Developmental toxicity Sprague Dawley Rats 25 ♀/group	Purity – 91.2% 0, 125, 375, 1125 mg/kg bw by gavage in corn oil on day 6–15 of gestation	**Maternal** **375** **Developmental** **375**	**Maternal effects:** **1125 mg/kg bw/day:** Clinical signs including excess salivation, urine stained abdominal fur, red exudate around mouth and/or nose, alopecia, rales, ungroomed coat, red exudate around vagina and decreased motor activity. Marginal ↓in bw, ↓bwg (gestation days 6–15) **Developmental effects:** **1125 mg/kg bw/day:** ↓litter weights, ↓ fetal body weights, Slight ↑ renal pelvic cavitation

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			Marginal ↓ in mean ossification sites per litter was observed, particular sites affected were the hyoid, caudal vertebrae, sternebral centres, xiphoid, forepaw metacarpals, digits and phalanges and the highpaw metatarsals and phalanges. A single incidence of an enlarged fontanelle was noted.
Developmental toxicity Hra: (NZW) Rabbits 20 ♀/group	Purity – 91.2% 0, 100, 300 or 1000 mg/kg bw/day by gavage in CMC on days 6–18 of gestation	**Maternal** **300** **Developmental** **300**	**Maternal effects:** **300 mg/kg bw/day:** ↓Food consumption over treatment period, ↓bwg over treatment period *-not considered adverse* **1000 mg/kg bw/day:** Mortality, abortions, ↑ frequency of abnormal faeces, ↓ bwg, ↓food consumption, ulcerations in the mucosal layer of the stomach and gall bladder **Developmental Data:** **300 mg/kg bw/day:** 3 fetuses (3 litters) with an incidence of intranasals (extra ossification sites between nasals). *-not considered adverse* **1000 mg/kg bw/day:** abortions
Genotoxicity Studies			
Ames test in *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538; *E. coli* strain WP2uvra	Purity – 91.2% 50, 158, 500, 1000, 1581, 3162, 5000 µg/plate in DMSO ± activation (S9)	Negative	
Gene mutation assay at HGPRT locus, cultured Chinese hamster ovary (CHO) cells	Purity 91.2% 0, 333, 1080, 1831, 2579, 3333 µg/ml in DMSO ± activation (S9)	With activation – negative Without activation, ↑ mutation frequencies at 2579 & 3333 µg/ml. Two repeat assays returned a significant increase in the mutagenic frequencies in one assay and no increase in a second assay. These results all occurred very close to the limit of solubility (3333 g/ml in DMSO)	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
In vitro chromosomal aberration frequencies in CHO cells	Purity – 91.2% 0, 1.25, 1.88, 2.0, 2.25, 2.5 mg/ml in DMSO (corrected for purity: 1.14, 1.71, 1.82, 2.05, and 2.28 mg/ml)	With activation – negative. Non-activated metabolic system, significant ($p<0.01$) increases in the number of chromosomally aberrant cells at (cytotoxic levels) 1.71 through 2.28 mg/ml in the 20hr harvest assay but not the 10 hr harvest.	
DNA repair; rat hepatocytic primary culture	Purity – 91.2% 0.13, 0.4, 1.3, 4, 13, 40, 133, 1333, 4000 µg/well	Cytotoxic at 4000 µg/well Results were negative based on the inability for the test compound to produce a mean nuclear grain count of five or greater then the vehicle control mean nuclear grain count at any level of concentration.	
Dominant Lethal study in Sprague Dawley Rats 10 ♂ 1 ♂ mated with 2 virgin ♀	Purity – 91.2% 0, 200, 1000, 2000 mg/kg bw/day by gavage for days	Negative	
In vivo Cytogenetics Assay in Sprague-Dawley rats 15/sex/group	Purity – 91.2% 0, 250, 800, 2500 mg/kg bw by gavage in corn oil	Negative	

NOTE: Effects noted above are known or assumed to occur in both sexes unless otherwise specified.

Table 2 Summary of Risk Assessment Endpoints

Exposure Scenario	Endpoint	Value	Study/NOAEL	CAF or MOE [a]
Acute Dietary	Not required due to low acute toxicity.			
Chronic Dietary	Decreased body weight	ADI = 0.56 mg/kg bw/day	2-year rat study NOAEL: 56 mg/kg bw/day	100
Inhalation [b] (Short/Intermediate Term)	Decreased body weight		13-week dog study NOAEL: 125 mg/kg bw/day	100
Dermal (Short/Intermediate Term)	Not established based on lack of toxicity in the dermal study and lack of other toxicological endpoints of concern.			

[a] CAF (composite assessment factor) refers to total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to desired margin of exposure for occupational or residential assessments.

[b] As an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Appendix IV Agricultural Mixer/Loader/Applicator and Postapplication Risk Assessment

Table 1 Inhalation Exposure Estimates and MOEs for Mixers/Loaders and Applicators of Products Containing Imazethapyr

USC[a]	Crop	Application Type	Formulation Type[b]	Max App Rate[c] (kg a.e./ha)	Area Treated[d] (ha/day)	Inhalation Exposure[e] (ug/kg/day)	Inhalation MOE[f] (Target = 100)
13,14	Alfalfa (established and seedling) for seed and forage	Farmer	WG	0.015	100	0.04	2.9×10^6
		Custom			300	0.13	9.8×10^5
		Farmer	WG in WSP	0.015	100	0.02	5.1×10^6
		Custom			300	0.07	1.7×10^6
		Farmer	SN	0.1008	100	0.37	3.4×10^5
		Custom			300	1.11	1.1×10^5
13,14	Imazethapyr tolerant corn	Farmer	SN	0.075	80	0.22	5.7×10^5
		Custom			300	0.38	3.3×10^5
13, 14	Field peas	Farmer	SN	0.05	100	0.18	6.8×10^5
		Custom			300	0.55	2.3×10^5
		Farmer	WG	0.015	100	0.04	2.9×10^6
		Custom			300	0.13	9.8×10^5
		Farmer	WG in WSP	0.015	100	0.02	5.1×10^6
		Custom			300	0.07	1.7×10^6
13, 14	Soybeans	Farmer	SN	0.1	100	0.37	3.4×10^5
		Custom			300	1.10	1.1×10^5
		Farmer	WG	0.1	100	0.28	4.4×10^5
		Custom			300	0.85	1.5×10^5
		Farmer	WG in WSP	0.1	100	0.16	7.7×10^5
		Custom			300	0.49	2.6×10^5
13, 14	Soybeans (Glyphosate tolerant); edible beans; snap beans	Farmer	SN	0.07488	100	0.27	4.6×10^5
		Custom			300	0.82	1.5×10^5
13, 14	Dry beans (pinto, pink, red)	Farmer	SN	0.05	100	0.18	6.8×10^5
		Custom			300	0.55	2.3×10^5
13, 14	Imazethapyr and imazamox tolerant canola	Farmer	SN	0.05	100	0.18	6.8×10^5
		Custom			300	0.55	2.3×10^5
		Farmer	WG	0.015	100	0.04	2.9×10^6
		Custom			300	0.13	9.8×10^5
		Farmer	WG in WSP	0.015	100	0.02	5.1×10^6
		Custom			300	0.07	1.7×10^6

USC[a]	Crop	Application Type	Formulation Type[b]	Max App Rate[c] (kg a.e./ha)	Area Treated[d] (ha/day)	Inhalation Exposure[e] (ug/kg/day)	Inhalation MOE[f] (Target = 100)
13, 14	Imazethapyr and imazamox tolerant lentils; fenugreek (for seed only)	Farmer	WG	0.015	100	0.04	2.9×10^6
		Custom			300	0.13	9.8×10^5
		Farmer	WG in WSP	0.015	100	0.02	5.1×10^6
		Custom			300	0.07	1.7×10^6
14	Processing peas; snow peas	Farmer	SN	0.07488	100	0.27	4.6×10^5
		Custom			300	0.82	1.5×10^5
14	Chickling vetch/grass pea	Farmer	SN	0.05	100	0.18	6.8×10^5
		Custom			300	0.55	2.3×10^5

Groundboom Application (open cab): Baseline PPE (long pants, long sleeved shirt and chemical resistant gloves) for mixer/loader

a USC = Use Site Category, USC 13 : Terrestrial Feed Crops, USC 14 : Terrestrial Food Crops

b SN = Solution, includes solutions and emulsifiable concentrate formulations; WG = wettable granules, includes wettable and soluble granule formulations, WSP = water soluble packaging

c Maximum listed label rate in kilograms of acid equivalent per hectare (kg a.e./ha)

d Area treated per day based on default values

e Where inhalation exposure µg/kg/day = (unit exposure × area treated × rate)/70 kg bw

f Inhalation MOE = NOAEL/inhalation exposure, based on an oral NOAEL of 125 mg/kg bw/day and target MOE of 100

Appendix V Dietary Exposure and Risk Estimates for Imazethapyr

Table 1 Aggregate Dietary (Food and Water) Exposure and Risk Estimates for Imazethapyr

Population Groups	Chronic DRA	
	Exposure (mg/kg bw/day)	% ADI
General Population	0.049611	8.9
All Infants (<1 year old)	0.085309	15.2
Children 1–2 years old	0.242825	43.4
Children 3–5 years old	0.159669	28.5
Children 6–12 years old	0.095536	17.1
Males 13–19 years old	0.043222	7.7
Males 20–49 years old	0.027808	5.0
Adults 50 + years old	0.025725	4.6
Females 13–49 years old	0.027987	5.0

DRA: Dietary risk assessment

ADI: Acceptable daily intake = 0.56 mg/kg bw/day based on a 2-year rat study

Conservative, unrefined residue data was used in the determination of the risk assessment.

Appendix VI Food Residue Chemistry Summary

1.1 Metabolism

The PMRA concluded that the residue chemistry database for imazethapyr in plants is complete, but it is incomplete for livestock. Nature and magnitude of the residue in plants and livestock are adequately understood. In all studies, the animal metabolism of imazethapyr was shown to proceed via oxidative hydroxylation of the ethyl group on the pyridine ring to form the hydroxyethyl analog CL 288511 similar as in the plant metabolism. However, in the plant metabolism this hydroxyethyl metabolite is then rapidly converted to the glucose conjugate CL 182704. Another metabolite identified but present in negligible amounts is the malonic acid ester of CL 182704.

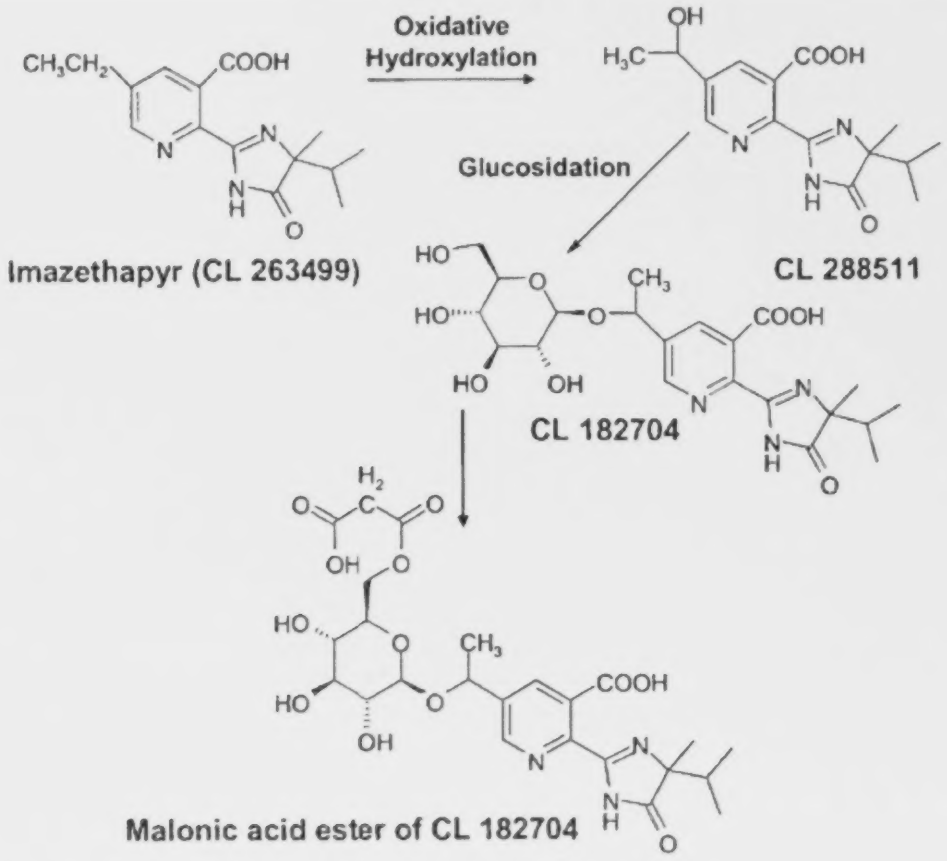
1.1.1 Plant metabolism

Imazethapyr contains a pyridine ring substituted with an ethyl group on the 5th position, a carboxylic acid on the 2nd position and an imidazolinone ring on the 3rd position. The mechanism of the selectivity of imazethapyr in tolerant species appears to their ability to rapidly metabolize the herbicide by oxidative hydroxylation at the α-carbon of the 5-ethyl substituent of the pyridine ring, followed by carbohydrate conjugation. Sensitive weed species metabolize imazethapyr slowly or not at all. The major metabolites for imazethapyr are derived from this oxidative hydroxylation of the ethyl group to form the hydroxyethyl analog CL 288511, followed by carbohydrate conjugation to form CL 182704, esterification of the carbohydrate conjugate, hydrolysis of the imidazolinone ring and decarboxylation of the pyridine ring.

The metabolic fate of imazethapyr has been presented for cereals (rice, corn), oilseeds (canola) and legumes (soybeans, peas, green beans and peanuts). The results of the three various crop types indicate that the metabolism of imazethapyr is similar and consistent. Regardless of the application timing or growth stage at application, residues of imazethapyr decline with time with little or no residues being detected in the seeds.

The results of the metabolic studies for the cereals show only small quantities of CL 263499 and CL 182704 while the major metabolite is CL 288511 which did not undergo further glycosidation. Contrary to the cereals, in the legume and oilseed crops the major metabolite was CL 182704. In alfalfa, further esterification of the glucoside compound occurred to form the malonic acid ester. According to the metabolism studies performed a proposed metabolic pathway for imazethapyr in the plants is shown in Appendix VI, Figure 1.

In treated plants most of the residues immediately after treatment were shown to be the parent compound. These residues declined later at harvest to non-detectable levels <0.05 ppm primarily due to metabolism but also dilution of residues by increasing biomass.



Appendix VI, Figure 1. Metabolism of imazethapyr in plants

Metabolic plant studies have shown that beside the parent compound, the hydroxy-metabolite CL 288511 and the glucosidic derivative CL 182704 can be found in significant concentrations in plant commodities. Appendix VI, Table 1 shows the radioactive labelled residue level found in the analysed crops.

Table 1 Radioactive Residue Level of Metabolites in Crops

Commodity	TRR (%)	
	CL 288511	CL 182704
Alfalfa	15%	45%
Soybeans	13%	51%
Peanuts	16%	56%
Dry peas	15%	40%
Corn	49%	6%
Green beans	ND	ND
Canola	ND	ND

ND: not detected
TRR: total radioactive residue

1.1.2 Animal metabolism

The animal metabolism studies were performed with the hydroxy-metabolite CL 288511 as the test compound in dairy cows, poultry and goats. In all studies, the animal metabolism of imazethapyr was shown to proceed via oxidative hydroxylation of the ethyl group on the pyridine ring to form the hydroxy-metabolite CL 288511 similar as in the plant metabolism. The results of all metabolism studies show a similar behaviour in all animal groups.

About 80–90% of the ingested pesticide is excreted (urine or feces) and only a small part is metabolized. Even when fed at exaggerated dose levels, the total residues in tissues, egg and milk were at the limit of detection of the analytical method (0.01 ppm) or slightly above at 0.09 ppm in goat kidneys. Characterization of the kidney and liver extracts by thin-layer chromatography and HPLC revealed that CL 288511 was the only significant component of the extractable radioactivity in both tissues.

As the animal metabolism studies were performed only with the metabolite and not with the parent compound, there are uncertainties about the metabolic profile of the residues in livestock commodities following the feeding with imazethapyr treated crops. Furthermore, as feed commodities can contain significant residue levels of the parent compound, confirmatory metabolism data are required to address the mentioned uncertainties.

1.1.3 Canadian and International

When pesticides are used on crops or when animals are fed crops treated with pesticides, residues may remain in or on the food when it is sold. PMRA must determine the amount of residues that are likely to remain in or on the food when the pesticide is used according to label directions and poses no unacceptable risks to human health. This amount is then legally established as the maximum residue limit (MRL) under the *Pest Control Products Act*. Pesticides that do not have established MRLs on food commodities are covered by the general MRL under subsection B.15.002 (1) of the Food and Drugs Regulation of the Food and Drugs Act (≤0.1ppm). A summary of imazethapyr Canadian and international MRLs are provided in Table 2. There are no MRLs for imazethapyr listed in the Codex Alimentarius.

Table 2 MRL and American Tolerances Summary

Commodity	Canadian MRL	American Tolerances
Vegetable, legume, group 6 (United States) Kidney beans, Lima beans, Navy beans, Pinto beans, Runner beans, Snap beans, Soybeans, Tepary beans, Wax beans, Peas (Canada)	0.1 ppm	0.1 ppm
Canola	0.05 ppm	0.1 ppm
Fenugreek	0.05 ppm	-
Peanut	-	0.1 ppm
Rice, bran	-	1.2 ppm
Rice, grain	-	0.3 ppm

Commodity	Canadian MRL	American Tolerances
Cattle, meat byproducts	-	0.1 ppm
Corn, field grain	-	0.1 ppm
Crayfish	-	0.15 ppm
Goat, meat byproducts	-	0.1 ppm
Hog, meat byproducts	-	0.1 ppm
Horse, meat byproducts	-	0.1 ppm
Sheep, meat byproducts	-	0.1 ppm
Endive (Regional American tolerance)	-	0.1 ppm
Lettuce, head (Regional American tolerance)	-	0.1 ppm
Lettuce, leaf (Regional American tolerance)	-	0.1 ppm

1.1.4 Residue Definition

The residue definition is used to describe the sum of the parent pesticide, its degradation products, metabolites and impurities that are of toxicological concern. All components of the residue definition will normally be included in the MRL expression of the pesticide, and residue analytical methods must be developed for all components of the residue definition.

The residue definition for imazethapyr is the parent compound, imazethapyr (CL 263499 or BAS 685 H) (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid, expressed as ammonium salt.

USEPA residue definition differs with the Canadian one, as it includes also metabolites CL 288511 and CL 182704 for certain commodities

1.2 Analytical Methods

1.2.1 Methods for Residue Analysis in Plant

Several analytical methods were developed to analyse imazethapyr residues in plant commodities. A summary of the submitted methods is presented in Appendix VI, Table 3.

Table 3 Summary of Residue Analytical Methods in Plant Commodities

Method code	Compound	Method	LOD (ppm)	Sample	Recovery %	PMRA #
M1981	CL 263499 CL 288511	GC-NSD	0.05	Corn	81–93 80–84	1156312
M1981	CL 263499 CL 288511	GC-NSD	0.05	Corn	78 73	1469345
M1984	CL 182704	GC-NSD	0.05	Corn	77–95	1156314
M1879*	CL 263499	N/S	0.01	Corn	86–101	1230959
M2143	CL 263499 CL 288511	GC-NSD	0.05	Corn oil, Meal	95 84	1469328
M2187	CL 263499 CL 288511	GC-NSD	0.05	Peas, Green or dry	85 87	1156316

Method code	Compound	Method	LOD (ppm)	Sample	Recovery %	PMRA #
M2186	CL 182704	GC-NSD	0.05	Peas, Green or dry	94	1156317
M1855	CL 263499	GC-NSD	0.1	Dry beans, Peas[1]	89 94	1142236
M2020	CL 263499 CL 288511	GC-NSD	0.05	Alfalfa	69–73 72–78	1159904
M2021	CL 182704	GC-NSD	0.05	Alfalfa	80–86	1159905
M1586	CL 263499	GC-NSD	0.1	Soybeans	84–90	1226656
M1586	CL 263499	GC-NSD	0.1	Soybeans	81–94	1469343
SOP M1993	CL 263499 CL 288511	GC-NSD	0.05	Soybeans	70–85 62–76	1236825
M3519	CL 263499 CL 288511 CL 182704	LC/MS; LC/MS/MS	0.05	Lentils	84–97;82–84 96–97;86 93–94;87–90	796066; 921920
M2422	CL 263499 CL 288511	GC-NPD	0.05	Canola oil or meal	100 94	1469338
M3319	CL 263499	LC/MS + Capillary electrophoresis	0.05	Canola seed	86	1469342
M2326*	CL 263499 CL 288511	GC-NPD	0.05	Canola seed	88 83	-
M1847*	-	GC/MS	0.1	Soybean	-	-
99-0996[2]	CL 263499 CL 288511	HPLC-MS	0.09 0.12	Peas	54–63 63	1373071
M2261	CL 263499 CL 288511 CL 182704	CE/UV HPLC/MS CE/UV	0.05	Alfalfa	86 96 85	USEPA
M1908.01	CL 263499 CL 288511 CL 182704	GC-NPD	0.05	Peanut hulls and meat	-	USEPA

* Incomplete data.

[1] Legumes – pinto beans, red kidney beans, split green peas, lima beans, snap beans, peas and pods.

[2] Method found to not be acceptable.

The submitted analytical methods are mainly GC-NSD or NPD methods that are based on extraction methods of the samples performed mainly with an acidic methanol:water mixture followed by an SPE/silica clean-up involving solvent partitioning and solid phase extraction. The samples are then analysed using a nitrogen sensitive or nitrogen-phosphorus sensitive. The results are usually calculated as CL 263499 or CL 288511 by the direct comparison of peak heights of those of external standards. The analysed metabolites are parent imazethapyr (CL 263499), the hydroxy metabolite (CL 288511) or the glucosidic ester (CL 182702) and the results show good recovery levels ranging from 52–127% and mean values from 62–101% (except the proposed method 99-0996) for LOD's from 0.05 to 0.1 ppm.

1.2.2 Methods for Residue Analysis of Food of Animal Origin

Analytical Method M3512 (PMRA# 796048) was developed in order to determine residues of CL 263499 (BAS 685 H) and its metabolite CL 288511, in crawfish though it was adapted and validated for the determination of residues in cow milk, cow tissue (liver, kidney, muscle and fat) and egg.

The parent compound CL 263499 and its metabolite CL 288511 are extracted from the animal tissues, milk and egg using a mixture of acetone/water/hydrochloric acid (25/74/1). An appropriate aliquot of the extract is reduced to dryness, the residue is then dissolved in water and the aqueous solution purified by an RP-18 solid phase extraction cartridge. The final determination is achieved by LC/MS. For confirmation of residues, a suitable LC/MS/MS method is available. The limit of quantitation (LOQ) of the method in all matrices (cow liver, kidney, fat, muscle, milk and eggs) is 0.01 ppm for each analyte.

Good recoveries of each analyte were obtained in cow matrices and egg over the fortification range tested, which was 0.01 ppm (LOQ) and 0.1 ppm for each analyte. The overall average recovery of CL 263499 in cow matrices and hen eggs was 85 ± 8%. The overall average recovery of metabolite CL 288511 in cow matrices and hen eggs was 87 ± 7%.

Another study of the M3512 method (PMRA# 796051) analyzed bovine kidney samples at LOQ=0.01 ppm. The LC/MS analysis resulted in recoveries of 94–124 % whereas, the LC/MS/MS analysis showed recoveries of 89–103%.

1.2.3 Independent Laboratory Validation

Independent laboratory validations were performed with good results for the residue analytical methods M1981, M2187, M1855, M1586, M2020, M3519, M2422, M3512 confirming the performance and validity of these residue analytical methods.

1.2.4 Multi-Residue Analytical Method

Imazethapyr, CL 288511 and CL 182704 tested for detection by United States Food and Drug Administration multi-residue methods as described in Transmittal 89-1 of the Pesticide Analytical Manual (PAM), Volume I. The components were not treated through Protocol A since they do not possess the N-methylcarbamate structure and do not fluoresce. Protocol B and C for acidic compounds were tested. Imazethapyr was the only compound that gave any significant chromatographic peaks after methylation. The methylated imazethapyr did not elute from the Florisil column in any of the fractions specified in Protocol B. Protocols D and E were not tested since the compounds being evaluated are polar and ionic.

Protocol B
The methyl ester reference standards do not exist for any of the three compounds being tested. Therefore, the esters were attempted to be prepared as stated in the procedure described in PAM I, Section 221.1. The methylation was shown to be quantitative using 2,4-D and methyl 2,4-D as model compounds. Imazethapyr was the only one of the three compounds tested that gave a significant GC peak as a result of the methylation procedure.

The Florisil column test was carried out in duplicate (reference PAM I, sections 121.33, 121.323 and 211.14(d)) using 200 mL portions of 6%, 15% and 50% diethyl ether in petroleum ether as the elution solvents from 20 g of re-activated Florisil PR. Standards of heptachlor epoxide, endrin and methylated CL 263499 (Protocol B) were placed on the columns. The GC chromatograms using an electron capture detector (Ni^{63}) and OV-101 column showed no methylated CL 263499 to be in any of the three eluates. In view of this, the method testing was terminated according to the directions in the referenced PAM I sections.

1.3 Food Residues

1.3.1 Storage Stability

1.3.1.1 Freezer Storage Stability in Plants

Several freezer stability studies were made for the analysis of the parent imazethapyr or its metabolites CL 288511 or CL 182704 and were reviewed by PMRA. A listing of the freezer stability studies depending on the analysed commodity is presented in Appendix VI, Table 4. The storage stability studies indicate a freezer storage stability for up to two years and were found acceptable for our assessment.

Table 4 Summary of Storage Stability Studies in Plants

Study	Metabolite	Commodity	Period (months)	Temp (°C)	Recovery (%)
1159902	Imazethapyr	Alfalfa forage/hay	24	-10/-20	
1064078	Imazethapyr	Alfalfa forage/hay	18	-10/-20	109 / 82
1469352	Imazethapyr	Soybean plant/seed/straw	24	-10/-20	85/86/86
921926	Imazethapyr	Peanut hulls/ nutmeat	25	-10/-20	81/74
921928	Imazethapyr	Corn forage, grain, fodder	24	-10/-20	74/91/73
921918	Imazethapyr	Rice straw, grain	24	-10/-20	81/82
796067	Imazethapyr	Lentil forage	22	-10/-20	90

The freezer storage stability studies cover most of the crop groups for the registered commodities. However, freezer stability studies might be required for green vegetables like snap beans, green beans or green peas as well as for fenugreek.

1.3.1.2 Freezer Storage Stability in Animals

As there are no submitted freezer stability studies in animal commodities. The registrant is requested to submit such studies.

1.3.1.3 Storage Stability of Working Solutions in Analytical Methodology

The studies found the calibration standard solution for imazethapyr (CL 263499) and its metabolites (CL 288511 and CL 182704), to be stable for at least 90 days in methanol and water when stored under refrigeration.

1.3.2 Crop Residues

Twenty-seven field trial studies were performed in Canada and 113 studies were performed in United States on registered crops and showed the magnitude of the imazethapyr residues in the treated crops. Samples from different commodities were taken and analysed. The summary of the determined residues is presented in Appendix VI, Table 5. The table presents the highest residue value found at the respective study application rate of imazethapyr. Many of the presented residue levels were obtained after a treatment at rates exceeding good agricultural practice.

Therefore, imazethapyr (CL 263499) residues in food commodities are not expected to exceed 0.1 ppm.

Table 5 Summary of Crop Residues

Crop	Commodity	CL 263499 (ppm)	CL 288511 (ppm)	CL 182704 (ppm)	Total (ppm)
Alfalfa	Forage	0.206	1.187	3.400	4.793
	Hay	0.050	0.940	7.000	7.990
	Plant	1.820	-	-	1.820
	Process meal	0.100	1.400	10.500	12.000
	Seed	0.050	0.050	0.050	0.150
Kidney beans	Green	0.100	-	-	0.100
	Dry	0.100	-	-	0.100
Navy beans	Green	0.100	-	-	0.100
	Dry	0.100	-	-	0.100
White beans	Dry	0.050	-	-	0.050
Lentils	Forage	0.050	0.050	0.225	0.325
	Seed	0.050	0.050	0.050	0.150
Peas	Dry seed	0.010	0.020	0.030	0.070*
	Vine	0.020	0.010	0.010	0.040*
	Pod	-	-	-	0.170*
	Hay	-	-	-	0.190*
Dry beans	Green	0.100	-	-	0.100
	Dry	0.100	-	-	0.100
Snap beans	Green	0.100	-	-	0.100
	Dry	0.100	-	-	0.100
	Plant	0.040	-	-	0.040
Soybeans	Plant	0.140	-	-	0.140
	Hull	-	-	-	0.040*
	Pod	0.170	-	-	0.170
	Seed	0.050	0.050	-	0.100
	Straw	0.340	-	-	0.340
Canola	Seed	0.050	0.050	-	0.100
Corn	Cob	-	-	-	0.009*
	Dry stalk	0.005	0.030	0.006	0.041
	Forage	0.050	0.050	0.050	0.150

Crop	Commodity	CL 263499 (ppm)	CL 288511 (ppm)	CL 182704 (ppm)	Total (ppm)
	Grain	0.050	0.058	0.050	0.158
	Meal	0.050	0.054	-	0.104
	Oil	0.050	0.050	-	0.100
	Silage	0.050	0.050	0.050	0.150
Field pea	Pod	0.050	0.050	0.050	0.150
	Seed	0.050	0.050	0.060	0.160
	Forage	0.050	0.050	-	0.100
	Vine	0.050	0.050	0.070	0.170
Green pea	Green pod	0.100	-	-	0.100
	Dry pod	0.100	-	-	0.100

* Total radioactive residue level

1.3.3 Livestock Residues

Eight livestock feeding studies were reviewed, three performed on lactating goats, two on lactating dairy cows and three on poultry. Two goat studies were performed with the parent compound CL 263499 at a feeding rate on 0.25 or 1.25 ppm and with the hydroxy-metabolite CL 288511 at a rate of 4.36 or 11 ppm. The residues were below the LOD (0.01 ppm or 0.05 ppm depending on the analysed commodity). The third study was performed with the hydroxy-metabolite at a rate of 42 ppm. Residues at the highest feeding rate were detected in kidney (0.09 ppm) and liver (0.02 ppm) with the rest of the commodities having residues below the LOD (0.0 ppm)

The dairy cow studies were performed both with the hydroxy-metabolite. In the first study done at a feeding rate of 27 ppm, no residues were detected in the analysed samples (0.01 ppm or 0.05 ppm depending on the analysed commodity). The second study was done at rates of 10 ppm, 30 ppm or 100 ppm. Detectable residues at the highest feeding rate were found in milk (0.014 ppm), fat (0.016 ppm) and kidney (0.06 ppm) with the rest of the samples being below the LOD of 0.01 ppm.

The feeding studies performed in poultry with the parent imazethapyr at a rate of 0.5 ppm or 2.5 ppm or with the hydroxy-metabolite at a rate of 0.62 ppm or 3.19 ppm were showing residue levels below the LOD (0.05 ppm). A third study done with the hydroxy-metabolite at a rate of 10.2 ppm had as well residues below the LOD (0.01 ppm).

According to the reviewed feeding studies, it is not expected to detect any residue of imazethapyr or its metabolites in any of the edible tissues, milk, blood or eggs when the livestock is fed with treated crops at good agricultural practice rate.

A summary of the highest residues detected in animal commodities from the reviewed studies is presented in Appendix VI, Table 6.

Table 6 Summary of Maximal Animal Residues

Livestock	Sample	Residue (ppm)	
		CL 263499	CL 288511
Goat	Milk	<0.01	<0.01
	Blood	<0.05	<0.05
	Fat	<0.05	<0.05
	Kidney	<0.05	0.09
	Liver	<0.05	<0.05
	Muscle	<0.05	<0.05
Cow	Milk	0.014	0.014
	Cream	-	<0.01
	Skimmed milk	-	<0.01
	Blood	-	<0.05
	Fat	-	<0.05
	Kidney	-	0.06
	Liver	-	<0.05
	Muscle	-	<0.05
Poultry	Blood	<0.05	<0.05
	Egg white	<0.05	<0.05
	Egg yolk	<0.05	<0.05
	Egg	-	<0.01
	Skin with fat	<0.05	<0.05
	Kidney	<0.05	<0.05
	Liver	<0.05	<0.05
	Muscle	<0.05	<0.05

1.3.3 Confined and Field Crop Rotation

After the treatment with imazethapyr, there is a high risk of yield loss with flax, corn, meadow, bromegrass, mustard, timothy and wheat seeded one year after application; with canola seeded up to two years later and sugarbeet and potato seeded up to three years after application. Legume crops and intermediate wheatgrass can be seeded the year of application with a low risk of yield loss. The intervals required by the recropping are limiting the use of imazethapyr for weed control in pea, alfalfa or dry edible beans in cropping sequences that include sugarbeet, canola or potato.

After the treatment with imazethapyr, the following crops can be grown safely the year after the application: tolerant corn, field peas, tolerant canola, tolerant lentils, spring wheat, winter wheat and durum wheat.

1.3.5 Processed Food/Feed Data

The processing study (PMRA# 1469526) presents the magnitude of the residues in processed corn grains. Processed corn grains, treated at level 5 fold than the registered application rate, present a residue level <0.05 ppm in CL 263499 and 0.054 in CL 288511. It is therefore expected that residue level in processed corn grains, which were treated at a nominal application rate, to show non-detectable levels of imazethapyr or its metabolite.

The following registered crops are used for industrial processing: corn, canola, peanut, soybean. The processing factors of the following commodities are:

Beef meat – dried	1.92-fold
Corn grain – syrup	1.5-fold
Peanut – butter	1.89-fold

Appendix VII Monitoring Data

A search for imazethapyr water monitoring data in Canada resulted in a number of samples with detection being reported. The federal, provincial and territorial representatives from all of the provinces and territories in Canada were contacted, requesting water monitoring data for imazethapyr along with other active ingredients currently under re-evaluation. In addition, requests were submitted to Environment Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada. Few responses were received. Any further data received as a result of this request will be considered and the information contained here will be updated, if necessary.

American databases were searched for detections of imazethapyr. Data on residues present in water samples taken in the United States are important to consider in the Canadian drinking water assessment given the extensive monitoring programs that exist in the United States. Runoff events, local use patterns, circumstantial hydrogeology as well as testing and reporting methods are probably more important influences on residue data rather than Northern versus Southern climate. As for the climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and inputs may be more numerous and frequent.

Data were available from the United States Geological Survey National Water Quality Assessment program (NAWQA) for both ground water and surface water.

Imazethapyr was detected in three drinking water prairie reservoirs and in treated waters of Alberta (surface or combination of surface and groundwater) at maximum concentrations of 0.0017 µg/L and 0.114 µg/L, respectively. Imazethapyr was also detected in rivers and in the St. Lawrence in the Quebec Province area with maximum concentrations of 0.84 µg/L and in small streams and Great Lakes of Ontario with maximum concentrations of 0.0048 µg/L and 0.0155 µg/L, respectively.

Imazethapyr was also found in water bodies that are unlikely to serve as drinking water sources. As such, three prairie wetlands showed maximum concentration of 0.09 µg/L.

Imazethapyr was also reported from groundwater studies conducted in the United States, where a maximum concentration of 0.236 µg/L was recorded in agricultural land use area. Rivers and reservoirs from the Midwestern United States also showed a maximum concentration of 0.74 µg/L.

An important limitation of the monitoring data set is that, in many cases, the data were not accompanied with use data for imazethapyr. For instance, the application rate, when the application occurred and weather conditions prior to sampling were not known or reported. Without this information, it is difficult to conclude if non-detects were a result of non-transport or more simply a result of inappropriate timing of sampling. In addition, because the data are sparse and concentrations vary in time and space, the maximum concentration reported is unlikely to be the absolute maximum concentration that would be observed in Canada. Factors that may result in higher concentrations being detected include application at higher rates, precipitation and some areas/soils are simply more prone to leaching and/or run off. Sampling at

intervals immediately following application would increase the likelihood that the maximum concentration would be detected.

Thus, it is likely imazethapyr was not used in some of the areas monitored and that higher concentrations of imazethapyr may occur in other areas not monitored. The imazethapyr monitoring data likely underestimate the peak exposure because of the following limitations:

I. In general, the data are sparse in both time and location. In some of the studies available, imazethapyr was analysed in samples that were taken from non-use areas. Imazethapyr use information from the areas surrounding where the samples were collected is often not available.

II. Sampling in some of the studies was conducted during periods when imazethapyr is not applied in Canada (that is, October through March).

III. The concentrations of pesticides in surface water are directly related to the frequency and timing of monitoring in relation to pesticide application and runoff events. Therefore, timing and frequency of sampling is likely to be the most important factor influencing the concentration detected and the frequency of detections. Samples are often taken at arbitrary time intervals (that is once a month, once a week) and are unlikely to capture the absolute maximum concentration of imazethapyr.

The scarcity of monitoring data in Canada and in United States does not allow for a clear estimation of the residues of imazethapyr in potential drinking water sources, especially groundwater, to be calculated through statistical analysis of monitoring data. The analysis of imazethapyr in Canadian waters has only been recently done due to analytical methodology limitations. The drinking water values currently available for use in the PMRA aggregate dietary risk assessment are those determined by the Level 1 water models.

Table 1 Summary of the Monitoring Studies Available for Imazethapyr

Reference	Location		Min Detection or Detection Limit (µg/L)	# of Systems Tested (or Absolute Number of Samples)	# of Systems or Samples With Detections	Detection Frequency (%)	Concentrations (µg/L)			
							Mean Detection	95th Percentile Detection	Absolute Max	Arithmetic Mean Including Non-detects at ½ LOD
Imazethapyr residues in municipal drinking water sources and ground water										
PMRA 1403269, 1311107, 1311110, 1311111, 1311112	Drinking water reservoirs in Manitoba	2003-2005	0.0012	NR	0	0	-	-	0	0.0006
	Drinking water reservoirs in Saskatchewan	2003-2005	0.0012	NR	NR	-	-	-	0.0008	0.0006
	Drinking water reservoirs in Alberta	2003-2005	0.0012	73	2	2.7	0.0015	0.0017	0.0017	0.0006
PMRA 1660533	Groundwater in the United States (1999-2007)	Urban land use	0.017–0.176	439	7	1.6	0.028	0.0704	0.0707	0.02
		Agricultural land use	0.01–0.0879	565	20	3.5	0.034	0.083	0.236	0.018
		Mixed land use	0.017–0.0879	542	7	1.3	0.031	0.116	0.156	0.025
		Other land use	0.017–0.0879	433	6	1.4	0.016	0.045	0.055	0.017
PMRA 1650553, 1311142	Alberta treated water survey program, treatment facilities, source by surface water, or a combination of surface water and groundwater (1995–2007)		0.02	1107	2	0.1	0.085	0.111	0.114	0.01
	Alberta treated water survey program, treatment facilities, source by groundwater only (1995-2007)		0.02	413	0	0	-	-	-	0.01
PMRA 1566596	Groundwater in Midwestern United States (1998)		0.01	25	4	16	-	-	0.059	-

Reference	Location	Min Detection or Detection Limit (µg/L)	# of Systems Tested (or Absolute Number of Samples)	# of Systems or Samples With Detections	Detection Frequency (%)	Concentrations (µg/L)			
						Mean Detection	95th Percentile Detection	Absolute Max	Arithmetic Mean Including Non-detects at ½ LOD
Imazethapyr residues in ambient water that may serve as a drinking water source									
PMRA 1398451, 1398452, 1398453	rivière Chibouet		2002	0.01	42	33	78.6	0.05	0.16	0.29	0.038
			2003	0.07	41	10	24.4	0.09	0.13	0.15	0.048
			2004	0.07	37	32	86.5	0.05	0.15	0.2	0.046
	rivière des Hurons		2002	0.01	42	26	61.9	0.03	0.07	0.19	0.023
			2003	0.07	41	3	7.3	0.1	0.1	0.1	0.040
	rivière Saint-Régis		2002	0.01	40	20	50	0.05	0.12	0.27	0.027
			2003	0.07	39	5	12.8	0.11	0.21	0.22	0.045
	rivière Saint-Zéphirin		2003	0.07	39	3	7.7	0.38	0.79	0.84	0.062
PMRA 1403269, 1311110, 1311111, 1311112, 1357366	Yamaska River		2004	0.0012	10	1	10	-	-	0.02	0.0025
	Saint-Lawrence at Levis		2004	0.0012	16	0	0	-	-	-	0.0006
	Ontario Region; areas of concern and small streams in the Niagara and Burlington area		2003	0.0012	171	9	5.3	0.003	0.0047	0.0048	0.0007
PMRA 1357368	Great Lakes Areas of Concern and connecting channels		2002	0.0012	59	0	0	-	-	-	0.0006
PMRA 1357369	Lake Huron tributaries		2002	0.0012	47	2	4.3	0.013	0.015	0.0155	0.0011
PMRA 1660492	Surface water in the United States (1999-2006)		Urban land use	0.017–0.176	359	23	6.4	0.03	0.12	0.13	0.018
			Agricultural land use	0.0085–0.04395	537	83	15.5	0.05	0.23	0.74	0.031
			Mixed land use	0.017–0.0879	456	49	10.7	0.03	0.11	0.19	0.024

Reference	Location	Min Detection or Detection Limit (µg/L)	# of Systems Tested (or Absolute Number of Samples)	# of Systems or Samples With Detections	Detection Frequency (%)	Concentrations (µg/L)						
						Mean Detection	95th Percentile Detection			Absolute Max	Arithmetic Mean Including Non-detects at ½ LOD	
	Other land use					0.017–0.0879	551	16	2.9	0.04	0.15	0.21	0.018
PMRA 1650553, 1311118	Alberta surface waters (1995-2007)					0.02	3991	32	0.8	0.091	0.171	0.409	0.011
PMRA 1566596	Rivers, reservoirs in Midwestern United States (1998)					0.01	130	92	70.8	-	-	0.689	-
Imazethapyr residues in ambient water unlikely to be used as a source of drinking water													
PMRA 1311116	Wetlands in Manitoba (2004)					0.0012	10	1	10	-	-	0.009	0.0015
	Wetlands in Saskatchewan (2004)					0.0012	30	0	0	-	-	-	0.0006
	Wetlands in Alberta (2004)					0.0012	20	0	0	-	-	-	0.0006

NR = Not recorded

Appendix VIII Environmental Fate and Toxicity

Table 1 Fate and Behaviour of Imazethapyr in the Environment

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products	Reference
Abiotic transformation						
Hydrolysis (25°C)	Imazethapyr	pH 5 (25°C) pH 7 (25°C) pH 9 (25°C) Pond water (25°C)	DT_{50}: Stable Stable 288 d Stable	Not a major route of transformation at environmentally relevant pH	2-[(1-carbamoyl-1, 2-dimethylpropyl) carbamoyl]-5-ethyl-nicotinic acid or CL 290395	PMRA 1583187 and PMRA 1226663
Phototransformation soil	Imazethapyr	Sandy loam soil, OM of 1% and pH 6.9	DT_{50}: 126 d	Not an important route of transformation	Not determined	PMRA 1130265
Phototransformation water	Imazethapyr	Unbuffered distilled water pH 5 pH 7 pH 9 (after 30 days)	DT_{50}: 1.9 d 1.8 d 2.1 d 2.4 d	A major route of transformation at environmentally relevant pH	5-Ethyl 3-pyridine carboxylic acid (or CL 290084) 5-Ethyl 2-3-pyridine carboxylic acid (or CL 271197)	PMRA 1130266
Biotransformation						
Soil – aerobic	Imazethapyr	Princeton sandy loam; 22–24°C	DT_{50}: 879 d	Persistent	Not determined	PMRA 1226746
		Sharkey silt clay; 25°C	DT_{50}: 216–318 d	Persistent	Not determined	PMRA 1682767
		Taloka silt loam; 25°C	DT_{50}: 198 d	Persistent	Not determined	
Soil – anaerobic	Imazethapyr	Princeton sandy loam 22–24°C (pH 5.3, OM 1.8%)	DT_{50}: stable	Persistent	Not determined	PMRA 1130267
Water/sediment – aerobic	Imazethapyr	Water: pH 8.33 and sediment: loamy sand, pH 7.7, OM 1.6%)	DT_{50}: 3387 d	Persistent. Imazethapyr predominantly found in the water column.	Not determined	PMRA 1232424
Water/sediment – anaerobic	Imazethapyr	Water: pH 8.33 and sediment: loamy sand, pH 7.7, OM 1.6%)	DT_{50}: 2803 d	Persistent	Not determined	PMRA 1232425

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products	Reference
Mobility Adsorption/ desorption	Imazethapyr	Four soils: pH 6.0–7.0; % OM 1.0 – 6.5; %clay 7.2–23.2	K_d: 0.41–0.74 K_{OC}: 21–102	Highly to very highly mobile	Not determined	PMRA 1226665
		Three soils: pH 7.0 – 8.1; % OC 0.5 – 3.1	K_d: 0.7–1.0 K_{OC} 54.1–164.5	Moderate to highly mobile	Not determined	PMRA 1682773
		17 soils: pH 4.2 – 8.3; % OC 0.3 – 3.4	K_d: 0.31–4.47 K_{OC} : 21.38–184.20	Nine soils: very highly mobile Two soils: highly mobile Three soils: moderately mobile Three soils : low mobility	Not determined	PMRA 1660316
		Seven soils: pH 4.3 – 8.0; % OC 0.35 – 8.51	K_d: 0.07–2.1 K_{OC} not determined	Moderately to highly mobility	Not determined	PMRA 1682377
		Six soils: pH 4.3 – 6.3; % OC 0.35 – 7.45	K_d: 0.08–0.76 K_{OC} not determined	Very highly mobile	Not determined	PMRA 1682769
Soil Thin layer Chromatography	Imazethapyr	Eight soils (5 Canadians, three U.S.A.)	Compared to five reference compounds	Mobile to very mobile, except for the Wisconsin silt loam from U.S.A.	Not determined	PMRA 1130292
Field dissipation (Canadian studies)	Imazethapyr	Vanscoy, Sask. Loam, pH 6.8, % OM 2.2	DT_{50}: 120–230 d	Moderately persistent to persistent	Not determined	PMRA 1146696
		Stirling, Alb. Clay loam, pH 6.6, % OM 2.9	DT_{50}: 281–309 d	Persistent	Not determined	PMRA 1146698
		Estlin, Sask. Clay, pH 7.6, % OM 3.1	DT_{50}: 83–115 d	Moderately persistent	Not determined	PMRA 1146695
		Charlottetown, PEI, Sandy loam, pH 5.8, % OM 2.9	DT_{50}: 19–47 d	Slightly to moderately persistent	Not determined	PMRA 1732086
		Kentville, NS. Sandy loam, pH 5.8, % OM 3.3	DT_{50}: 34–63 d	Slightly to moderately persistent	Not determined	PMRA 1732086
		Georgetown, On. Sandy loam, pH 6.0, % OM 2.5	DT_{50}: 90–287 d	Moderately persistent to persistent	Not determined	PMRA 1130293
		Georgetown, On. Clay loam, pH 6.5, % OM 3.0	DT_{50}: 143–250 d	Moderately persistent to persistent	Not determined	PMRA 1226749
		Georgetown, On. Clay loam, pH 6.2, OM 6.0	DT_{50}: 56–146 d	Moderately persistent	Not determined	PMRA 1226750

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products	Reference
Field dissipation (U.S. studies)	Imazethapyr	York, Nebr. Silt loam, pH 5.3, % OM 4.2	DT_{50}: 73–124 d	Moderately persistent	Not determined	PMRA 1226749 PMRA 1226750
		Webster, Iowa. Loam, pH 5.8, % OM 3.1	DT_{50}: 159–221 d	Moderately persistent to persistent	Not determined	PMRA 1130276 PMRA 1130277 PMRA 1130278

Table 2 Toxicity of Imazethapyr to Non-Target Species

Organism	Study Type	Species	Test material	Endpoint	Value (Effect)	Effect of Concern	Reference
Terrestrial Species							
Invertebrate	Acute contact	Honey bee (*Apis mellifera*)	Technical	96-h LD_{50}	>100 µg a.e./bee	Mortality	PMRA 1226686
	Acute contact	Earthworm (*Eisenia foetida*)	Technical	14-d LC_{50}	>15.7 mg a.e./kg soil	Mortality	PMRA 1130294
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	Technical	21-d LD_{50}	>2150 mg a.e./kg bw	Mortality	PMRA 1226669
		Mallard duck (*Anas platyrhynchos*)		21-d LD_{50}	>2150 mg a.e./kg bw	Mortality	PMRA 1226670
	Acute dietary	Bobwhite quail (*Colinus virginianus*)		8-d LC_{50}	>5000 mg a.e./kg diet	Mortality	PMRA 1226671
		Mallard duck (*Anas platyrhynchos*)		8-d LC_{50}	>5000 mg a.e./kg diet	Mortality	PMRA 1226673
	Reproduction	Bobwhite quail (*Colinus virginianus*)		22-week LC_{50} 20 wks NOAEL	>2000 mg a.e./kg diet >1200 mg a.e./kg diet	Mortality Reproduction Performance	PMRA 1130283 PMRA 1468487
		Mallard duck (*Anas platyrhynchos*)		22-week LC_{50} 20 wks NOAEL	>2000 mg a.e./kg diet >1200 mg a.e./kg diet	Mortality Reproduction Performance	PMRA 1130282 PMRA 1468490

Organism	Study Type	Species	Test material	Endpoint	Value (Effect)	Effect of Concern	Reference
Mammals	Acute	Mice	Technical	LD_{50}	>5000 mg a.e./kg bw	No clinical adverse signs	N/A
		Rats			>5000 mg a.e./kg bw		
		Rabbits			>5000 mg a.e./kg bw		
	Subchronic dietary	Rats	Technical	13 weeks NOEL	779 mg a.e./kg bw/day for male 427 mg a.e./kg bw/day for female	Decreased body weight and body-weight gain	
	Chronic	Rat	Technical	2-year NOAEL	56 mg a.e./kg bw/day for male >447 mg a.e./kg bw/day for female	Uterine effects (increase in haemosiderin deposits and others)	N/A
		Rats	Technical	2-generation NOAEL	**Parental** a.e./kg bw/day for male mg a.e./kg bw/day for female **Reproduction** 937 mg a.e./kg bw/day for male **Offspring** 485 mg a.e./kg bw/day for male	Increased haemosiderin deposits and a single incidence of an endometrical stromal polyp of the uterus/cervix at the high dose	N/A
Plants	Seedling emergence	Onion (*Allium cepa*, monocotyledon	Technical	EC_{25} NOEC	>1.1 g a.e./ha 1.1 g a.e./ha	Plant dry weight	PMRA 1639350
		Cabbage (*Brassica oleracea*, dicotyledon) Tomato (*Lycopersicon esculentum*, dicotyledon)		EC_{25} NOEC	3.5 g a.e./ha 1.1 g a.e./ha	Plant height	
	Vegetative vigor	Onion (*Allium cepa*, monocotyledon)	Technical	EC_{25}	>12.3 g a.e./ha	Plant dry weight	PMRA 1639348

Organism	Study Type	Species	Test material	Endpoint	Value (Effect)	Effect of Concern	Reference
		Onion (*Allium cepa*), corn (*Zea may*), perennial ryegrass (*Lollium perenne*, monocotyledon)		NOEC	8.7 g a.e./ha		
	Vegetative vigour	Tomato (*Lycopersicon esculentum*, dicotyledon)		EC_{25} NOEC	1.8 g a.e./ha 0.55 g a.e./ha	Plant dry weight	
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	Technical	48-h LC_{50} NOEC	>1000 mg a.e./L 1000 mg a.e./L	Immobility	PMRA 1226682
			2ASU formulation (purity of 22.2%)	EC50 NOEC	>24.2 mg a.e./L 24.2 mg a.e./L	Mortality	PMRA 1469553
	Chronic	*Daphnia magna*	Technical	NOEC LOEC	103 mg a.e./L >103 mg a.e./L	Mortality	PMRA 1468472
Fish	Acute	Bluegill sunfish (*Lepomis macrochirus*)	Technical	96-h LC_{50} NOEC	420 mg a.e./L 320 mg a.e./L	Mortality	PMRA 1226675
		Rainbow trout (*Oncorhynchus mykiss*)	Technical	96-h LC_{50} NOEC	340 mg a.e./L 100 mg a.e./L		PMRA 1226680
		Channel catfish (*Ictalurus punctatus*)	Technical	96-h LC_{50} NOEC	240 mg a.e./L 180 mg a.e./L		PMRA 1226678
	Chronic	Fathead minnow (*Pimephales promelas*)	Technical	NOEC	14 mg a.e./L		PMRA 1226753
				NOEC LOEC	97 mg a.e./L >97 mg a.e./L		PMRA 1468480
Algae	Acute	Green algae	Technical	EC_{50}	71 mg a.e./L		PMRA 1226206

Organism	Study Type	Species	Test material	Endpoint	Value (Effect)	Effect of Concern	Reference
		(*Selenastrum capricornutum*)		NOEC	50 mg a.e./L	Biomass and growth rate	
			2ASU formulation (purity of 22.2%)	ErC_{50} , EbC_{50} NOEC	>22.4 mg a.e./L 22.4 mg a.e./L		PMRA 1469506
		Blue-green algae (*Anabaena flos-aquae*)	2ASU formulation (purity of 22.2%)	96-h EC_{50} NOEC	>4.8 mg a.e./L 1.6 mg a.e./L		PMRA 1469559
		Diatom, (*Navicula pelliculosa*)	2ASU formulation (purity of 22.2%)	96-h EC_{50} NOEC	>22.9 mg a.e./L 22.9 mg a.e./L		PMRA 1469558
Vascular Plants	Acute	Duck weed (*Lemna gibba*)	Technical	14-d EC_{50} NOEC	0.0101 mg a.e./L 0.00438 mg a.e./L	Frond number	PMRA 1142242
Marine Organisms							
Invertebrates	Acute	Saltwater mysid (*Mysidiopsis bahia*)	Technical	96-h LC_{50} NOEC	>114 mg a.e./L 114 mg a.e./L	Mortality	PMRA 1468473
Bivalve	Acute	Eastern Oyster (*Crassostrea virginica*)	Technical	96-h LC_{50} NOEC	>109 mg a.e./L 109 mg a.e./L	Shell deposition	PMRA 1468474
Fish	Acute	Sheepshead minnow (*Cyprinodon variegatus*)	Technical	96-h LC_{50} NOEC	>112 mg a.e./L 112 mg a.e./L	Mortality	PMRA 1468478
Algae	Acute	Diatom (*Skeletonma costatum*)	2ASU formulation (purity of 22.2%)	96-h LC_{50} NOEC	>23.1 mg a.e./L 23.1 mg a.e./L	Growth rate	PMRA 1469557

N/A = Not available
2 ASU = 240 g/L of aqueous solution with urea (formulation code by the company)

Table 3 Summary of Screening Level Risk Assessment of Imazethapyr to Terrestrial Invertebrates and Plants

Organism	Exposure	Endpoint reported	EEC	RQ*	LOC exceeded
Honeybee	Acute contact	LD_{50} = 112 kg a.e./ha	0.1 kg a.e./ha	9.0×10^{-4}	No
Earthworm	Acute	LC_{50} 7.85 mg a.e./kg soil	0.004 mg a.e./kg soil	5.1×10^{-4}	No
Plants	Onion (*Allium cepa*)	EC_{25} = 1.1 g a.e./ha	30 g a.e./ha**	**27.3**	Yes

*Risk quotients (RQ) shown in bold exceed the level of concern (RQ >1)
** Lowest rate of application

Table 4 Refined Risk Assessment of Imazethapyr to Terrestrial Plants

Organism	Exposure	Endpoint values*	Application method	Drift EEC** (g a.i/ha)	RQ***	LOC exceeded
Plants	Onion (*Allium cepa*)	EC_{25} = 1.1 g a.e./ha	Ground boom	6.0	**5.45**	Yes
		HC_5 = 4.04 g a.e./ha			**1.49**	Yes

* A species sensitivity distribution (SSD) approach was used to determine the endpoint of 5% hazardous concentration (HC_5) to protect 95% of terrestrial plants.

** EECs takes into consideration the spray drift deposition of spray quality of ASAE medium for ground (6%) at 1 m downwind from the site of maximal application rate of 100 g a.e./ha.

*** Risk quotients shown in bold exceed the level of concern (RQ >1).

Table 5 Screening Level Risk Assessment of Imazethapyr to Birds and Mammals

Organism	Exposure*	Endpoint** (mg a.i/kg body weight/day)	Food guild	EDE (mg a.i/kg body weight/day)	RQ***	LOC Exceeded
Birds						
Small (20 g)	Acute Oral LD_{50}	215	Insectivore	5.05	2.3×10^{-2}	No
			Granivore	0.87	4.0×10^{-3}	No
			Frugivore	2.60	1.2×10^{-2}	No
	Dietary LC_{50}	28.3	Insectivore	5.05	1.8×10^{-1}	No
			Granivore	0.87	3.1×10^{-2}	No
			Frugivore	2.60	9.2×10^{-2}	No
	Reproduction NOEC	113.1	Insectivore	5.05	4.5×10^{-2}	No
			Granivore	0.87	8.0×10^{-3}	No
			Frugivore	2.60	2.3×10^{-2}	No
Medium (100 g)	Acute Oral LD_{50}	215	Insectivore	3.94	1.8×10^{-2}	No
			Granivore	0.68	3.0×10^{-3}	No
			Frugivore	2.03	9.0×10^{-3}	No
	Dietary LC_{50}	28.3	Insectivore	3.94	1.4×10^{-1}	No
			Granivore	0.68	2.4×10^{-2}	No
			Frugivore	2.03	7.1×10^{-2}	No
	Reproduction NOEC	113.1	Insectivore	3.94	3.5×10^{-2}	No
			Granivore	0.68	6.0×10^{-3}	No
			Frugivore	2.03	1.8×10^{-2}	No
Large (1000 g)	Acute Oral LD_{50}	215	Insectivore	1.15	5.0×10^{-3}	No
			Granivore	0.20	9.0×10^{-4}	No
			Frugivore	0.59	3.0×10^{-3}	No
			herbivore	7.16	3.3×10^{-2}	No

Organism	Exposure*	Endpoint** (mg a.i/kg body weight/day)	Food guild	EDE (mg a.i/kg body weight/day)	RQ***	LOC Exceeded
	Dietary LC_{50}	28.3	Insectivore	1.15	4.1×10^{-2}	No
			Granivore	0.20	7.0×10^{-3}	No
			Frugivore	0.59	2.1×10^{-2}	No
			herbivore	7.16	2.5×10^{-1}	No
	Reproduction NOEC	113.1	Insectivore	1.15	1.0×10^{-2}	No
			Granivore	0.20	2.0×10^{-3}	No
			Frugivore	0.59	5.0×10^{-3}	No
			herbivore	7.16	6.3×10^{-2}	No
Mammals						
Small (15 g)	Acute oral LD_{50}	500	Insectivore	2.90	5.8×10^{-3}	No
			Granivore	0.50	1.0×10^{-3}	No
			Frugivore	1.50	3.0×10^{-3}	No
	Subchronic 13 week Dietary NOEL 427	427	Insectivore	2.90	8.0×10^{-3}	No
			Granivore	0.50	1.0×10^{-3}	No
			Frugivore	1.50	3.0×10^{-3}	No
			Herbivore (leaves and leafy crops)	18.07	4.0×10^{-2}	No
			Herbivore (short grass)	10.35	2.4×10^{-2}	No
			Herbivore (long grass)	6.32	1.5×10^{-2}	No
			Herbivore (forage crops)	9.50	2.2×10^{-2}	No
Medium (35 g)	Acute oral LD_{50}	500	Insectivore	2.49	5.0×10^{-3}	No
			Granivore	0.43	1.0×10^{-3}	No
			Frugivore	1.28	3.0×10^{-3}	No
	Subchronic 13 week Dietary NOEL 427	427	Insectivore	2.49	6.0×10^{-3}	No
			Granivore	0.43	1.0×10^{-3}	No
			Frugivore	1.28	3.0×10^{-3}	No
			Herbivore (leaves and leafy crops)	15.49	3.6×10^{-2}	No
			Herbivore (short grass)	8.88	2.1×10^{-2}	No
			Herbivore (long grass)	5.42	1.3×10^{-2}	No

Organism	Exposure*	Endpoint** (mg a.i/kg body weight/day)	Food guild	EDE (mg a.i/kg body weight/day)	RQ***	LOC Exceeded
			Herbivore (forage crops)	8.15	1.9×10^{-2}	No
Large (1000 g)	Acute oral LD_{50}	500	Insectivore	1.36	3.0×10^{-3}	No
			Granivore	0.23	7.0×10^{-4}	No
			Frugivore	0.70	1.0×10^{-3}	No
	Subchronic 13 week Dietary NOEL: 427	427	Granivore	1.36	3.0×10^{-3}	No
			Frugivore	0.23	5.0×10^{-4}	No
			Insectivore	0.70	2.0×10^{-3}	No
			Herbivore (leaves and leafy crops)	8.46	2.0×10^{-2}	No
			Herbivore (short grass)	4.85	1.0×10^{-2}	No
			Herbivore (long grass)	2.96	7.0×10^{-3}	No
			Herbivore (forage crops)	4.45	1.0×10^{-2}	No

* Risk quotient for reproduction in birds were obtained from PMRA# 1130282 and PMRA# 1130283. Endpoints presented in PMRA# 1468487 and PMRA# 1468490 would not exceed the LOC.

** Acute oral and dietary endpoints that were originally expressed as a concentration (mg a.e./kg diet) have been converted to daily dose (mg a.e./kg body weight/day) and further divided by a factor of 10 in order to address differences in species sensitivity.

*** Risk quotients shown in bold exceed the level of concern (RQ >1)

Table 6 Summary of Screening Level Risk Assessment of Imazethapyr to Aquatic Organisms

Organism (Species)	Exposure	Test substance	Endpoint value (mg a.e./L) ÷ safety factor*	EEC (mg a.e./L)**	RQ***
Freshwater species					
Invertebrate: *Daphnia magna*	Acute	TGAI	48-hour LC_{50} >1000 ÷ 2 = 500 NOEC = 1000	80 cm depth = 0.0125 80 cm depth = 0.0125	1.0×10^{-3}
	Chronic	TGAI	NOEC = 103 LOEC > 103	80 cm depth = 0.0125 80 cm depth = 0.0125	1.2×10^{-4}
		2ASU formulation (pure 22.2%)	48-hour EC_{50} >24.2 ÷ 2 = 12.1 NOEC = 24.2	80 cm depth = 0.0125 80 cm depth = 0.0125	1.0×10^{-3} 5.0×10^{-4}
Cold fish: Rainbow trout *Onchorynchus mykiss*	Acute	TGAI	96-hour LC_{50} = 340 ÷ 10 = 34.0 NOEC = 100	80 cm depth = 0.0125 80 cm depth = 0.0125	3.7×10^{-4} 1.3×10^{-4}

Organism (Species)	Exposure	Test substance	Endpoint value (mg a.e./L) ÷ safety factor*	EEC (mg a.e./L)**	RQ***
Warm fish:, Bluegill sunfish, *Lepomis macrochirus*	Acute	TGAI	96-hour LC_{50} = 420 ÷ 10 = 42.0 NOEC = 320	80 cm depth = 0.0125 80 cm depth = 0.0125	3.0×10^{-4} 3.9×10^{-5}
Channel catfish, *Ictalurus punctatus*	Acute	TGAI	96-hour LC_{50} = 240 ÷ 10 = 24.0 NOEC = 180	80 cm depth = 0.0125 80 cm depth = 0.0125	5.2×10^{-4} 6.9×10^{-5}
Fathead minnow *Pimephales promelas*	Early Life Stage	TGAI	NOEC = 14.0	80 cm depth = 0.0125	8.9×10^{-4}
		TGAI	NOEC = 97 LOEC > 97	80 cm depth = 0.0125	1.3×10^{-4}
Algae: Green algae, *Selenastrum capricornutum*	Acute	TGAI	EC_{50} = 71 ÷ 2 = 35 NOEC = 50	80 cm depth = 0.0125 80 cm depth = 0.0125	3.6×10^{-4} 2.5×10^{-4}
		2ASU formulation (pure 22.2%)	ErC_{50} and EbC_{50} >22.4 ÷ 2 = 11.2 NOEC = 22.4	80 cm depth = 0.0125 80 cm depth = 0.0125	1.1×10^{-3} 5.6×10^{-4}
Blue-green algae, *Anabaena flos-aquae*	Acute	2ASU formulation (pure 22.2%)	96-hour EC_{50} >4.8 ÷ 2 = 2.4 NOEC = 1.6	80 cm depth = 0.0125 80 cm depth = 0.0125	5.2×10^{-3} 7.8×10^{-3}
Diatom: *Navicula pelliculosa*	Acute	2ASU formulation (pure 22.2%)	96-hour EC_{50} >22.9 ÷ 2 = 11.5 NOEC = 22.9	80 cm depth = 0.0125 80 cm depth = 0.0125	1.0×10^{-3} 5.4×10^{-4}
Vascular plant: *Lemna gibba*	Dissolved	TGAI	14-day EC_{50}=0.0101 ÷ 2 = 0.00505 NOEC = 0.00438	80 cm depth = 0.0125 80 cm depth = 0.0125	**2.5** **2.9**
Amphibians: Surrogate fish: Fathead minnow	Chronic	TGAI	35-d NOEC = 14.0	15 cm depth = 0.067	4.0×10^{-3}
Marine species					
Saltwater mysid, *Mysidiopsis bahia*	Acute	TGAI	96-hour LC_{50} >114 ÷ 2 = 57 NOEC = 114	80 cm depth = 0.0125 80 cm depth = 0.0125	8.9×10^{-4} 1.1×10^{-3}
Shell deposition, Eastern oyster, *Crassostrea virginica*	Acute	TGAI	96-hour EC_{50}>109 ÷ 2 = 54.5 NOEC = 109	80 cm depth = 0.0125 80 cm depth = 0.0125	2.3×10^{-4} 1.1×10^{-4}
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Acute	TGAI	96-hour LC_{50} >112 ÷ 10 = 11.2 NOEC = 112	80 cm depth = 0.0125 80 cm depth = 0.0125	1.1×10^{-3} 1.1×10^{-4}

Organism (Species)	Exposure	Test substance	Endpoint value (mg a.e./L) ÷ safety factor*	EEC (mg a.e./L)**	RQ***
Algae: diatom *Skeletonema costatum*	Acute	2ASU formulation (pure 22.2%)	96-hour EC_{50} >23.1 ÷ 2 = 11.6	80 cm depth = 0.0125	1.1×10^{-3}
			NOEC = 23.1	80 cm depth = 0.0125	5.4×10^{-4}

2 ASU = 240 g/L of aqueous solution with urea (formulation code by the company)
*Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
** EEC based on a 15 cm water body depth for amphibians and an 80 cm water depth for all other aquatic organisms.
*** Values in bolt character have a RQ >1.

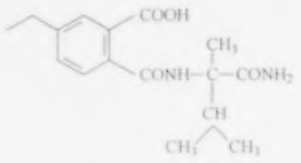
Table 7 Risk Quotient for Aquatic Vascular Plants Obtained From Spray Drift of Imazethapyr Used at Maximum Rate of Application

Parameters	Soybean (0.100 kg a.e./ha)
Duckweed (Lemna gibba) (EC_{50} mg a.e./L ÷ 2)	0.00505
EEC in 80 cm deep water body (0.0125 mg a.e./L × 0.06)	0.00075
RQ	1.49×10^{-1}

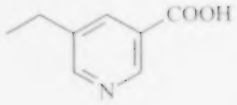
Table 8 Risk Quotient for the Aquatic Vascular Plant *Lemna gibba* Determined for Imazethapyr in Run-off from Water Modeling (PRZM-EXAM)

Province	Application Rate (g a.e./ha)	Target Crop	EC_{50} ÷ 2 (mg a.e./L)	EEC: 90th percentile of 21 day average (mg/L)	RQ (EEC/ EC_{50} ÷ 2)
Atlantic	100	Soybean	0.005	0.0009	1.8×10^{-1}

Diagram 1 Major transformation Products of Imazethapyr



Compound CL 290,395
2-[(1-carbamoyl-1,2-dimethylpropyl) carbamoyl]-5-ethyl-nicotinic acid



Compound 290,084
5-Ethyl 3-pyridine carboxilic acid

Table 9 Toxic Substances Management Policy Considerations—Comparison to Track 1 Criteria for Imazethapyr

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Imazethapyr Are criteria met?	Transformation Products Are criteria met?
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act**	Yes		Yes	Not available
Predominantly anthropogenic**	Yes		Yes	Not available
Persistent	Persistent in one of the following media:		Persistent in Soil and water/sediment system.	Not available
	Soil	Half-life ≥182 days	270–879 days at 24–25°C	Not available
	Water	Half-life ≥182 days	2803–3387 days	Not available
	Sediment	Half-life ≥365 days	2803–3387 days	Not available
	Air	Half-life ≥2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (8.5×10^{-8} Pa at 25°C) and Henry's Law Constant (1.7×10^{-13} atm.m^3/mole).	Not available
Bioaccumulative	The log L_{OW} and/or BCF and/or BAF are preferred over log K_{OW}.		Not bioaccumulative	Not available
	Log $K_{OW} \geq 5$		1.49 at pH7	Not available
	BCF ≥ 5000		<5000	Not available
	BAF ≥ 5000		Not available	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	Not expected to meet TSMP Track 1 criteria.

*All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (that is all other TSMP criteria are met).

**The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

Appendix IX Label Amendments for Products Containing Imazethapyr

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

The labels of end-use products in Canada must be amended to include the following statements to further protect workers and the environment.

Add to ENVIRONMENTAL HAZARDS:

> TOXIC to non-target terrestrial and aquatic plants. Observe buffer zones specified under DIRECTIONS FOR USE.

For the end-use product Valor-1 only:

> This product contains aromatic petroleum distillates which are toxic to aquatic organisms.

The following is required as a standard label statement for runoff:

> To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil or clay.
>
> Avoid application when heavy rain is forecast.
>
> Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Add to DIRECTIONS FOR USE:

For all formulations:

> Do not enter or allow entry into treated areas during the restricted-entry interval of 12 hours.
>
> Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

DO NOT apply by air

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of Application	Crop	Buffer Zones (metres) Required for the Protection of:	
		Freshwater Habitat	Terrestrial habitat
Field sprayer	All crops	1	1

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

References

A. Information Considered for the Chemistry Assessment

Studies/Information Submitted By Applicant/Registrant (Unpublished)

PMRA Document Number: 1468387
Reference: 1987, Pesticide Assessment Guidelines and Subdivision Product Chemistry Description of Beginning Materials and Manufacturing Process for the Manufacturing-Use Product AC 263499 Section 61-2, US-MRID40429401, MRID: 40429401, Data Numbering Code: 2.11.2, 2.11.3 Confidential Business Information.

PMRA Document Number: 1468396
Reference: 2000, Chemical Composition Data for AC 263499 Imazethapyr Technical Grade Active Substance (2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-ethyl nicotinic acid) to Support Registration in Canada, APBR 1121, MRID: N/A, Data Numbering Code: 2.13.1, 2.13.2, 2.13.3 Confidential Business Information.

PMRA Document Number: 1468401
Reference: 1998, Composition and Identification of AC 263499 Imazethapyr Technical Grade Active Substance 2-4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl-5-ethyl nicotinic acid for Reregistration in Argentina, APBR 951, MRID: N/A, Data Numbering Code: 2.13.3 Confidential Business Information.

PMRA Document Number: 1468402
Reference: 1987, Physical and Chemical Characteristics for the Manufacturing-Use Product, AC 263,499, US-CHDV Volume 27 Report No. 10, MRID: N/A, Data Numbering Code: 2.14.1, 2.14.10, 2.14.11, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9 Confidential Business Information.

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B. Information Considered for the Toxicological Risk Assessment

Studies/Information Provided by Applicant/Registrant (Unpublished)

PMRA Document Number: 1226693
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PMRA Document Number: 1226695
Reference: 1985, AC 263, 499: Eye Irritation Study In Albino Rabbits, Data Numbering Code: 4.2.4

PMRA Document Number: 1226684
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Reference: 1985, AC 263,499: Skin Irritation Study In Albino Rabbits, Data Numbering Code: 4.2.5

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Reference: 1985, Acute Inhalation Toxicity, Single Level, 4-hour Exposure - Rats, Data Numbering Code: 4.2.3

PMRA Document Number: 1226035
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PMRA Document Number: 1236464
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Reference: 1985, Herbicide AC 263,499: The Absorption, Excretion, Tissue Residues, And Metabolism Of Carbon-14 Labeled AC 263,499 In The Rat., Data Numbering Code: 4.5.9,6.4

PMRA Document Number: 1226644
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PMRA Document Number: 1226033
Reference: 1985, Teratology Study With AC 263,499 In Rats, Data Numbering Code: 4.5.2

PMRA Document Number: 1226027
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Reference: 1986, AC 263, 499: Toxicology Report Ax85-1 A 13-week Rat Feeding Study. Experiment L-2139., Data Numbering Code: 4.3.1

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Reference: 1986, Summary - AC 263,499 Rat Oral LD50, Data Numbering Code: 4.2.1

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Reference: 1986, Summary Of Experimental Results - Rat Oral LD50 CL 288,511, Data Numbering Code: 4.2.1

PMRA Document Number: 1226029
Reference: 1986, Two-generation (two-litter) Reproduction Study With AC 263, 499 In Rats (Vol. I Of V), Data Numbering Code: 4.5.1

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Additional Information Considered

Published Information

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PMRA Document Number: 1728447
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C. Information Considered for the Occupational Risk Assessment

Additional Information Considered

Published Information

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Reference: US EPA, 2002. ID#s - 6F04746 (nongrass animal feed crop group), IE06286 (import tolerance; imidazolinone-tolerant canola) and 0F0 Health Effects Division (HED) Risk Assessment for Imazethapyr. US EPA Office of Prevention, Pesticides and Toxic Substances, Washington, DC. April 23, 2002. Data Numbering Code: 12.5.

D. Information Considered for the Dietary Risk Assessment

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Reference: (Imazethapyr/2AS): Residues Of CL263,499 In Green Peas (Succulent And Dry) (c-3149;09414;0185;pu-88-wa-02(6950);1808)(Pursuit), Data Numbering Code: 7.4.2

PMRA Document Number: 1146682
Reference: (Imazethapyr/2AS): Residues Of CL263,499 In Green Peas (Succulent And Dry)(c-3174;09414;0185;pu-88-mn-05(7054);1831)(Pursuit), Data Numbering Code: 7.4.2

PMRA Document Number: 1146683
Reference: (Imazethapyr/2AS): Residues Of CL263,499 In Green Peas (Succulent And Dry)(c-3177;09414;0185;pu-88-md-01(7149);1851)(Pursuit), Data Numbering Code: 7.4.2

PMRA Document Number: 1146687
Reference: (Imazethapyr/2AS): Residues Of CL263,499 In Green Peas (Succulent And Dry)(c-3181;09414;0185;pu-88-mn-01(7056);1841)(Pursuit), Data Numbering Code: 7.4.2

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PMRA Document Number: 1233298
Reference: 5.3 Crop Residue Data, Anajysis Of Canadian Soybean Samples, Data Numbering Code: 7.4.2

PMRA Document Number: 1146692
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PMRA Document Number: 1784706
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PMRA Document Number: 1146335
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PMRA Document Number: 1146334
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PMRA Document Number: 1159903
Reference: CL263,499(Imazethapyr/2AS): Residues Of CL263,499;cl288,511 And Cl182,704 In Alfalfa Forage And Hay (Post;cn;1992)(res93-167;0952;pu92cn05;8013;0533)(Pursuit), Data Numbering Code: 7.4.2

PMRA Document Number: 1159904
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PMRA Document Number: 1159905
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PMRA Document Number: 1159063
Reference: CL288,511: Carbon14 CL288,5511-derived Residues In Blood,milk And Edible Tissues Of Lactating Goats (Pd-m Volume 27-20;m88a511pt2;89jun26;09415;l-2361;0184)(Pursuit), Data Numbering Code: 7.5

PMRA Document Number: 1159907
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PMRA Document Number: 1146332
Reference: Imazethapyr Herbicide (CL 263,499): Residues And Metabolism Of Carbon-14 Labeled CL 263,499 In Corn (Pd-m Volume 27-9;09415;0462)(Pursuit), Data Numbering Code: 6.3

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PMRA Document Number: 1156316
Reference: Imazethapyr: Validation Of GC Method M-2187 For The Determination Of CL263,499 And CL288,511 (hydroxy Metabolite) Residues In Pea Vine,hay,succulent Pod,straw, And Dry Pea (c3786;0952;pu91pt04;0185)(Pursuit), Data Numbering Code: 6.3

PMRA Document Number: 1146679
Reference: Metabolism Of Carbon-14 Labeled CL263,499 In Peas Under Field Conditions (met-93-004;m88p499pt1;0951;0187)(Pursuit), Data Numbering Code: 6.3

PMRA Document Number: 796064
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PMRA Document Number: 1226365
Reference: Pursuit (CL 263, 499/ipa-as) : Residues Of CL 263, 499 In Soybean Green Plant, Soybean Dry Plant & Soybean Seed (Pe; Ont, 1984) (c-2851), Data Numbering Code: 7.4.2

PMRA Document Number: 1226366
Reference: Pursuit (CL 263, 499/ipa-as) : Residues Of CL 263, 499 In Soybean Green Plant, Soybean Dry Plant & Soybean Seed (Post; Ont, 1984) (c-2846), Data Numbering Code: 7.4.2

PMRA Document Number: 1226364
Reference: Pursuit (CL 263, 499/ipa-as) : Residues Of CL 263, 499 In Soybean Seed (Pe; Ont, 1984) (c-2822.1), Data Numbering Code: 7.4.2

PMRA Document Number: 1226362
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PMRA Document Number: 1226363
Reference: Pursuit (CL 263, 499/ipa-as) : Residues Of CL 263, 499 In Soybean Seed (Post; Ont, 1984) (c-2826.1), Data Numbering Code: 7.4.2

PMRA Document Number: 1161080
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Reference: Summaries Pursuit Herbicide (AC 263,499): Study Of The Absorption, Excretion, And Metabolism In Rats Receiving An Oral Dose Of About 1,000 Mg/kg Carbon-14 Labeled AC 263,499, Pyridine-6 Carbon-14 AC 263,499-drived Residues In Soybeans After Postemergence,

PMRA Document Number: 1230959
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PMRA Document Number: 1182981
Reference: Table I: Summary Of CL 263,499 Residues In Dry Beans (Pinto Beans), And Navy Beans, Data Numbering Code: 7.1

PMRA Document Number: 1056105
Reference: Tables - Summary Of Residue Data For Legume Vegetable Group Except Soybean, Summary Of Residues In Peas, Summary Of Residues In Soybeans, Data Numbering Code: 7.2.1

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PMRA Document Number: 921918
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PMRA Document Number: 1064078
Reference: 1995, Imazethapyr (CL 263,499): Freezer Stability of Residues of CL 243,499 and its Metabolites, CL 288,511 and CL 182,704 in Alfalfa Forage and Hay, Data Numbering Code: 7.3

PMRA Document Number: 921929
Reference: 2000, CL 263499 (Imazethapyr): Freezer Storage Stability of Residues of CL 263499 and Metabolites CL 288511 and CL 182704 in Rice Straw and Grain, Data Numbering Code: 7.3

PMRA Document Number: 1146484
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PMRA Document Number: 1146486
Reference: CL 263499 (Imazethapyr/2AS) Residues Of CL 263,499 And CL 288,511 In Allelix Canola Seed (RES93-187;0952;PU92cn07;8045;0533)(Pursuit For Western Canada), Data Numbering Code: 7.4.2

PMRA Document Number: 1469369
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PMRA Document Number: 1146483
Reference: Imazethapyr (CL263,499): Metabolism Of Carbon-14 Labeled CL 263,499 In Field Grown Canola (MET93-023;SC920084;M92P499NDL) Final Report (Pursuit For Western Canada), Data Numbering Code: 6.3

Additional Information Considered

Published Information

PMRA Document Number: 1685251
Reference: Moyer J.R., and Esau R., (1996), Imidazolinone Herbicide Effects on Following Rotational Crops in Southern Alberta, *Weed Technology*, Vol. 10, pp 100-106. Data Numbering Code: 7.4.4.

PMRA Document Number: 1685252
Reference: Roberts T.R., Hutson D. H., Jewess P. J., (1998), *Metabolic Pathways of Agrochemicals: Herbicides and Plant Growth Regulators*, Royal Society of Chemistry (Great Britain), Information Services, pp 372-376. Data Numbering Code: 6.1.

E. Information Considered for the Environmental Risk Assessment

Studies/Info Provided by the Applicant/Registrant (Unpublished)

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PMRA Document Number: 1146694
Reference: Summaries: Cl263,499 (Imazethapyr)(Pursuit), DACO: 8.1.

PMRA Document Number: 1168682
Reference: Supplemental Information Provided by Cyc in Response to P.Delorme (EAD) Request for Additional Information of July 23 1996 [Imazamox (AC 299,263)/Odyssey (Imazamox + Imazethapyr)](Attachements + Correspondence Together), Daco: 8.1.

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Reference: Imazethapyr (CL 263,499) Summaries: Residues of CL 263, 499 in Soils. 2 Field Studies in Ontario Evaluated Soil Dissipation and Leaching Potential., DACO: 8.1.

PMRA Document Number: 1232423
Reference: 1990, Summmaries - Aerobic and Anaerobic Aquatic Metabolism of 14C-AC 263,499, the Active Ingredient in Pursuit Herbicide., DACO: 8.1.

PMRA Document Number: 1130264
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PMRA Document Number: 1226664
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PMRA Document Number: 1226731
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PMRA Document Number: 1130267
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PMRA Document Number: 1226666
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PMRA Document Number: 1226746
Reference: 1987, Pursuit Herbicide (AC 263,499): A Laboratory Aerobic Soil Metabolism Study of Pyridine Ring-6 Carbon-14 Labelled AC263,499 in Sandy Loam Soil, DACO: 8.2.3.1.

PMRA Document Number: 1231904
Reference: AC 263,499 (Pursuit) Anaerobic Aquatic Metabolism (N-162-3) Revised November 22, 1988, DACO: 8.2.3.1.

PMRA Document Number: 1226662
Reference: 1984, AC 263,499: The Hydrolysis of Carbon-14 Labelled AC 263,499 in Pond Water. The Hydrolysis of Carbon-14 Labeled AC 263,499 in Buffered Aqueous Solution. Determination of the Partition Coefficient in N-Octanol/Water Systems. Soil Adsorption and Desorption.

PMRA Document Number: 1231903
Reference: AC-263,499 (Pursuit) Aerobic Aquatic Metabolism (N-162-4) Revised November 22, 1988, DACO: 8.2.3.5.2.

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Reference: 1989, Imazethapyr (AC 263,499): Soil Thin-Layer Chromatography, E-89-11, DACO: 8.2.4.1.

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PMRA Document Number: 1168338
Reference: CL 299,263: Soil Dissipation Study with CL 299,263 in Michigan. (MI;1994).(Res96-019;0952;Xp94mi01;8272). (Odyssey). American Cyanamid Company, Princeton, New Jersey. Study Finalized: August 15.

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PMRA Document Number: 1146696 (Imazethapyr): Residues of CL 263,499 in soil Located in Central Saskatchewan (C3791;09418;Pu90cn04;7619;0532)(Pursuit), DACO: 8.3.2.3.

PMRA Document Number: 1146698
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PMRA Document Number: 1166286
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PMRA Document Number: 1237493
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PMRA Document Number: 1226206
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PMRA Document Number: 1226674
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PMRA Document Number: 1226687
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Reference: 1985, Static Bioassay Procedure for Determining the Acute Toxicity of Chemical Substances to Freshwater Fish (Rainbow Trout), 33057, DACO: 9.5.2.1, 9.5.5.

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PMRA Document Number: 1130283
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PMRA Document Number: 1583187
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PMRA Document Number: 1130276
Reference: 1987. Pursuit® herbicide (CL 263,499): Residues of CL 263,499 in soil (PPI; IA, 1985) (C-2951), Cyanamid, Report No. C-3006. 31 p. DACO: 8.3.2.3.

PMRA Document Number: 1130277
Reference: 1987. Pursuit® herbicide (CL 263,499): Residues of CL 263,499 in soil (PRE; IA, 1985) (C-2951), Cyanamid, Report No. C-3008. 29 p. DACO: 8.3.2.3.

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